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ORGANIC SEMINAR ABSTRACTS

1968-69

Semester I

Department of Chemistry and Chemical Engineering

University of Illinois

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I Semester 1968-69

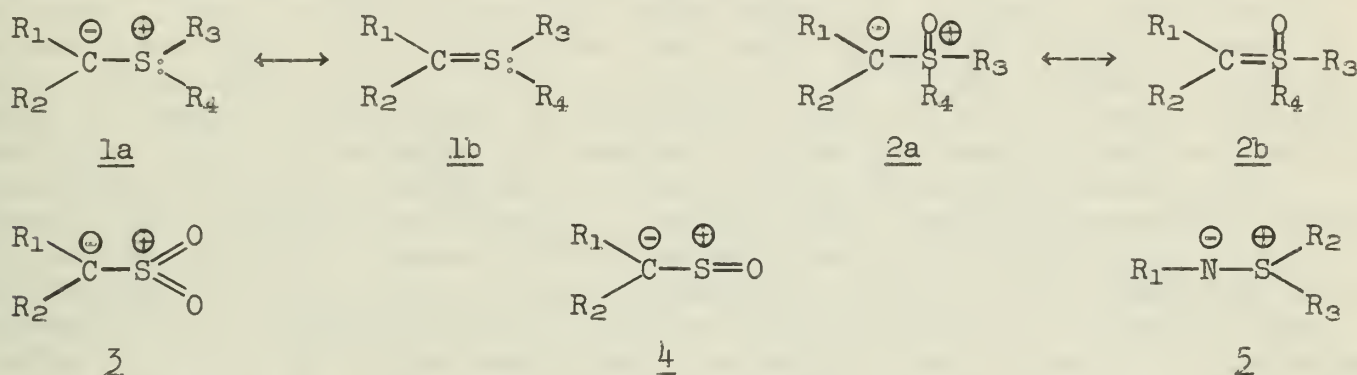
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RECENT SULFUR YLIDE CHEMISTRY

Reported by A. Harry Andrist

September 16, 1968

The intention of this seminar is to review the advances in the chemistry of sulfur ylides (1, 2) reported since the appearance of A. W. Johnson's excellent book, which covers the literature through January, 1966.^{1a} Subsequent reviews²⁻⁵ have not extended literature coverage beyond that of Johnson's monograph. The chemistry of sulfenes (3),^{6,7} sulfoxes (4),⁷ and iminodisulfuranes (5)⁷ has been recently reviewed and will not be discussed here.



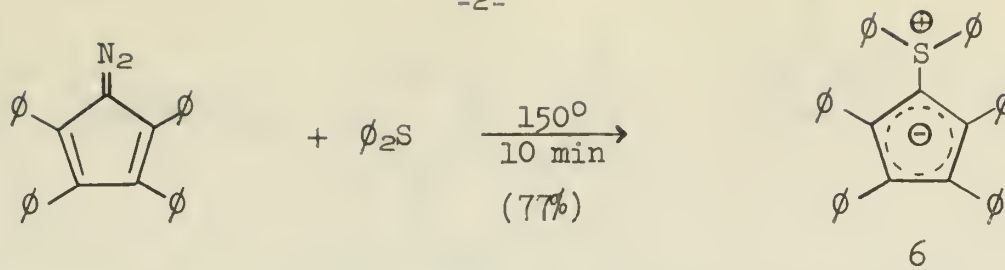
Development of the well-known Wittig reaction brought about a search for other heteroatoms, like phosphorus, which are capable of stabilizing an adjacent carbanion. The intense activity in sulfur ylide chemistry began shortly after it seemed apparent that the sulfonium group provided more stabilization for an α -carbanion through valence shell expansion, i.e. $d\pi-p\pi$ overlap (1b, 2b), than phosphonium, arsonium, or ammonium groups.^{1b,8,9}

PREPARATION OF SULFUR YLIDES

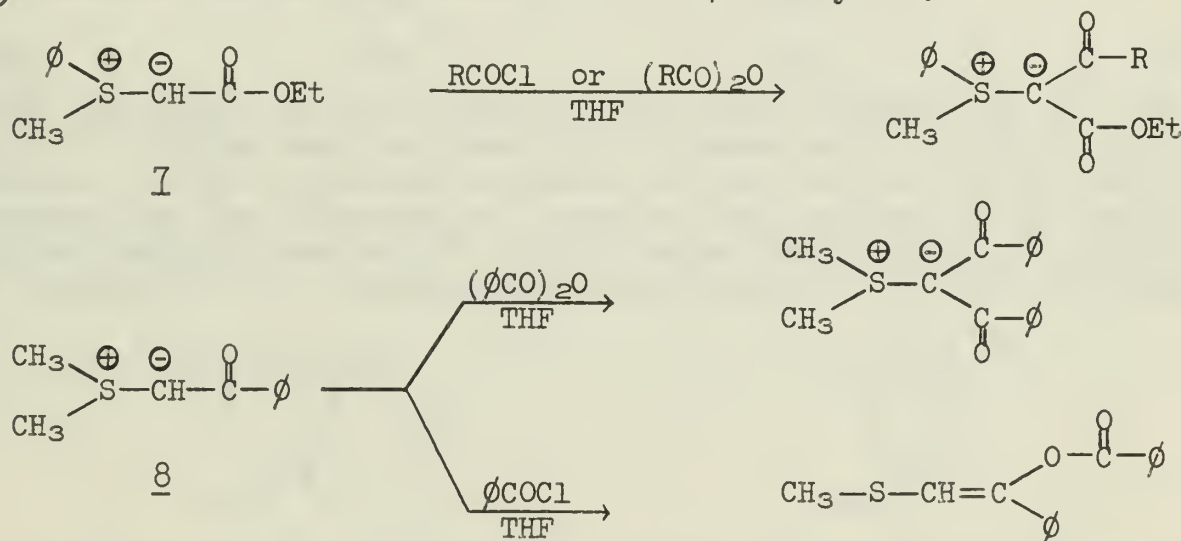
The method first employed to generate sulfonium ylides, treatment of the corresponding sulfonium salt with a base of suitable strength, has maintained its status as the most widely applied procedure. If R_1 and R_2 in the conjugate acid of 1 are electron withdrawing, the ylide can be prepared upon mild base treatment and may be of sufficient stability to permit isolation. When R_1 and R_2 are electron releasing, much stronger bases are required, e.g. sodium hydride, phenyllithium, or alkyllithiums. Corey has found that the sterically crowded lithium reagents, e.g. *t*-butyllithium, are superior to the *n*-alkyllithiums for generation of unstable sulfonium ylides, and further that dichloromethylithium in dimethoxyethane is the reagent of choice.^{10,11}

The use of strong base sometimes imposes serious limitations on the preparation and subsequent reactions of an ylide. The following highly promising new methods have been employed to prepare sulfonium ylides in the absence of base: (1) reaction of dialkyl sulfides¹² and thiocarbonyl compounds¹³ with activated oxiranes, (2) acid or thionyl chloride catalyzed condensation of sulfoxides with activated methylene compounds or activated halides,^{12,14,15} (3) acetic anhydride or phosphorus pentoxide catalyzed condensation of sulfoxides with active methylene compounds,¹⁵⁻²¹ and (4) treatment of reactive methylene compounds with dicyclohexylcarbodiimide (DCC) and dimethyl sulfoxide (DMSO) in the presence of anhydrous phosphoric acid.²² Activating groups thus far have included keto, ester, nitrile, amide, and phosphonate functions. The DMSO-DCC reaction (4) appears to be the most reactive system since it has afforded sulfonium ylides in good yields which are unavailable by way of the other procedures.

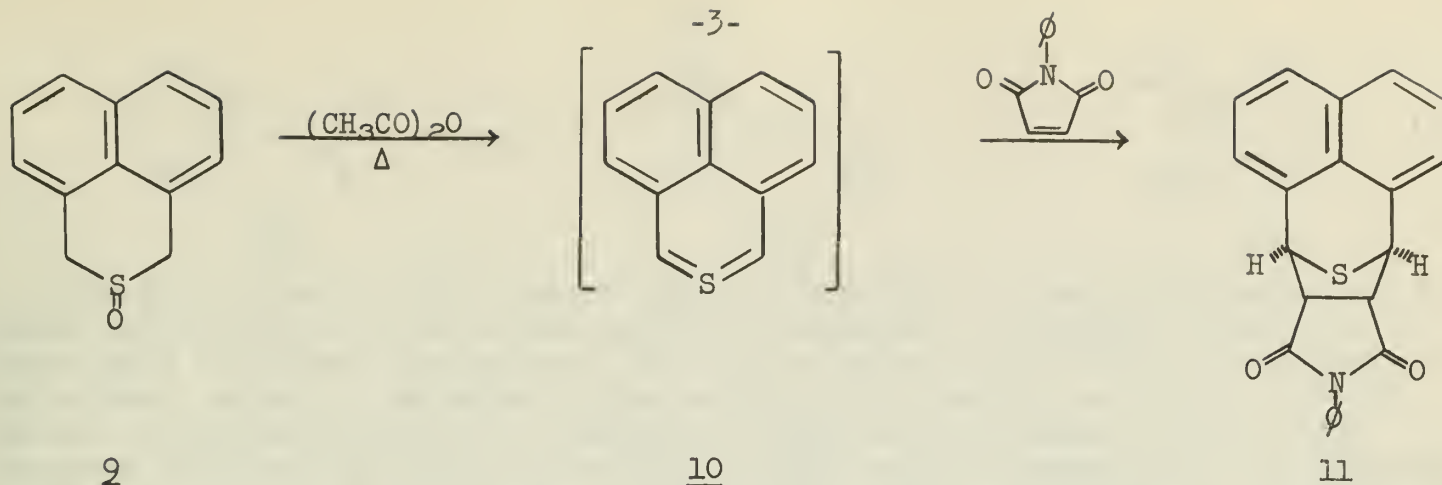
The addition of alkylphenylsulfides to benzyne continues to be a useful procedure for the preparation of diphenylsulfuranes (1, $R_3=R_4=\phi$). The synthesis of sulfonium ylides via carbenes has yet to be shown to possess the same utility as the corresponding synthesis of phosphonium ylides.^{1c} Although there is good evidence for the intermediacy of sulfonium ylides in the attack of carbenes on sulfides,²³⁻²⁵ only recently has a stable sulfurane (6) been isolated from such a reaction:²⁶



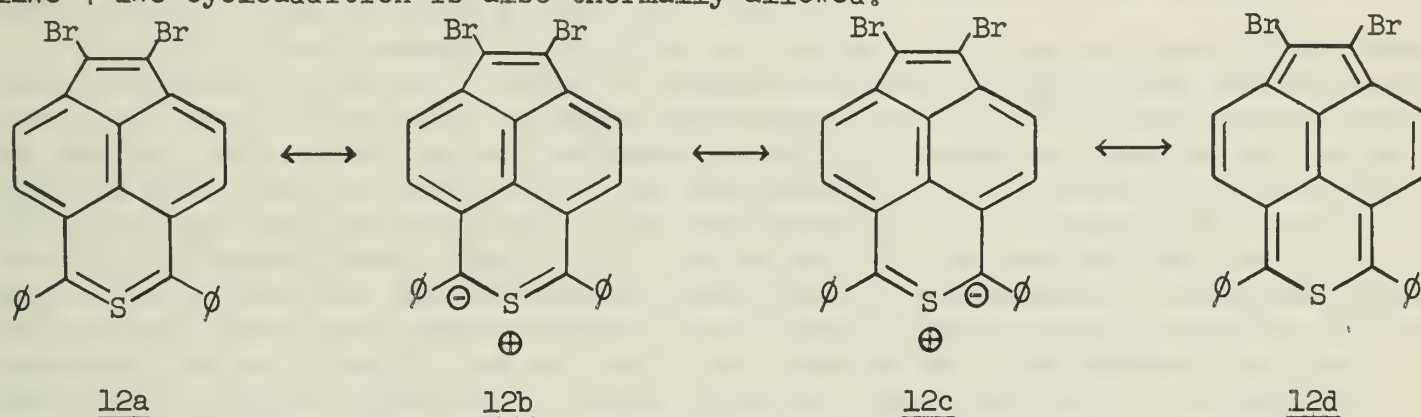
Other successful phosphonium ylide preparations which have not yet been extended to the synthesis of sulfonium ylides include: (1) addition of nucleophilic reagents to vinyl 'onium salts,^{1c} (2) addition of simple ylides to olefins,^{1c} (3) pyrolysis of azines,^{1c} and (4) electrolysis of 'onium halides.²⁷ However, alkylation and acylation of simple sulfur ylides have been shown to provide valuable routes to complex ylides with a large variety of substrates.²⁸⁻³⁴ The ambident nature of the anion in β -ketosulfonium ylides is reflected in the over-all course of acylation reactions. By way of example, the mono-anion of methyl phenacyl sulfone³³ underwent O-acylation with benzoyl chloride in ether, ethanol, and in *t*-butanol, while phenacylidene dimethyloxysulfurane (2, $R_1 = \text{CO}\phi$, $R_2 = \text{H}$, $R_3 = R_4 = \text{CH}_3$) underwent C-acylation with benzoyl chloride in benzene.³⁴ Moreover, β -ester sulfonium, e.g. 7, and sulfoxonium ylides underwent exclusive acylation at carbon with either acid chlorides or anhydrides in tetrahydrofuran,³⁰ but the site of acylation on phenacylidene-dimethylsulfurane (8) in the same solvent varied with the nature of the acylating agent, i.e. 8 gave C-acylation with benzoic anhydride and O-acylation with benzoyl chloride.^{31,32} By analogy with acylations of β -ketophosphoranes³⁵ it appears that the benzoyl chloride acylation reaction is kinetically-controlled while acylation with benzoic anhydride is thermodynamically-controlled. As pointed out by Johnson and Amel,³² the 3d-orbitals of sulfur and the carbonyl function in 8 compete in delocalizing the carbanion, and the extent of C- or O-acylation reflects the extent of this delocalization. Thus acylation of the above phenacylides is rationalized by the fact that increased positive charge on sulfur, i.e. effectively increased $d_{\pi}-p_{\pi}$ overlap, decreases the enolate character of the β -keto ylide.³²



The transient existence of a new type of tetravalent sulfur intermediate (10, 2-thiaphenalene) has been postulated independently by Cava^{36,37} and Schlessinger.^{38,39} The highly reactive sulfonium ylide 10 was generated by dehydration of the corresponding sulfoxide (9) and was trapped as the N-phenymaleimide adduct (11). The isomeric episulfide of 10 was later isolated and under identical conditions was shown not to undergo the cycloaddition with N-phenylmaleimide.⁴⁰ The above novel cycloaddition reaction (10 \rightarrow 11) is a Diels-Alder-type reaction, i.e. a $4\pi e + 2\pi e$ process, and on the basis of orbital symmetry⁴¹ is allowed to be concerted even though the charge-separated resonance hybrid (1a) may be the principal contributor to the wave equation of 10. For this reason it would be of ancillary interest to know the stereochemistry of adducts from both *cis* and *trans* dienophiles. It should be noted that 10 is not analogous to a cyclic allenic system since $d_{\pi}-p_{\pi}$ bonding has little if any angular requirement^{42,43} and also completely defies Bredt's rule.⁴⁴



Most recently Ponticello and Schlessinger report the isolation of a stabilized tetravalent sulfur heterocycle (12) which is thermally stable to 130°. Presumably there is aromatic property by resonance stabilization of 12. The nmr spectrum reported indicates an aromatic system. The possibility exists, however, that the divinyl sulfide 12d is not a mesomeric form of the ylide 12a,b,c if a significant change in geometry is involved. The expected N-phenylmaleimide adduct⁴⁵ is formed from 12, but one could also envisage its formation exclusively from 12d since the 12π + 2π cycloaddition is also thermally allowed.⁴¹

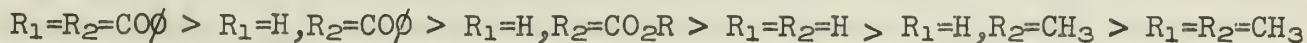


Three derivatives of a new aromatic sulfur ylide system, e.g. 13, have been prepared.^{46,47} Unlike the non-crystalline thiabenzenes,^{1a} the thiabenzene 1-oxides are remarkably stable crystalline compounds and thus have been more completely characterized than the thiabenzenes. Moreover, the structure of 13 was verified by X-ray crystallographic analysis.⁴⁸ König reported the isolation of 14 after treatment of benzonitrile with methylene dimethyloxysulfurane (2, R₁=R₂=H, R₂=R₃=CH₃).⁴⁹

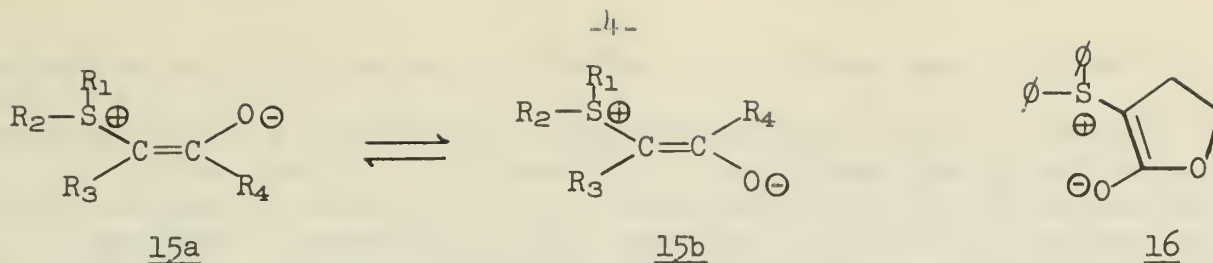


PHYSICAL PROPERTIES OF SULFUR YLIDES

The thermal, oxidative, and solvolytic stabilities of dimethylsulfonium ylides (1, R₃=R₄=CH₃) vary considerably with structure:



β-Keto sulfonium ylides (1, R₁=COR) characteristically exhibit a carbonyl infrared frequency 110-140 cm⁻¹ lower than that of the corresponding sulfonium salt, presumably owing to the importance of the enolate betaine configuration (15).^{21,22,30,50} Since the lactone ylide 16 gave a similar carbonyl shift as did the acyclic ylides, the *cis* enolate configuration (15a) appears to be the favored isomer.³⁰ Moreover, infrared data suggest that in β,β-diketo sulfonium ylides only one carbonyl group is involved in stabilizing the ylide.³⁰



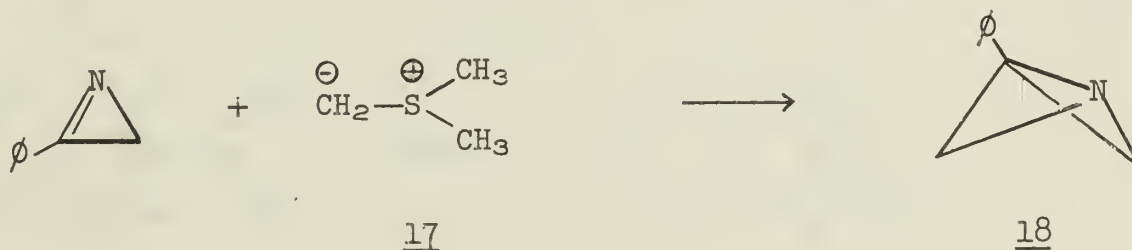
For 15 ($R_1=R_2=CH_3$, $R_3=H$) the nmr spectra show sharp, temperature-independent S-methyl absorptions, but the methine proton is broadened, presumably owing to an appreciable rotational barrier about the carbon-carbon bond.^{21,50,51} Two pieces of nmr evidence support a pyramidal sulfur atom in β -keto sulfonium ylides: the nmr spectra of 15 ($R_3=COCH_3$) give a pronounced temperature dependence for the $COCH_3$ resonance,^{21,52} and 15 ($R_1=R_4=\phi$, $R_2=CH_2\phi$, $R_3=NH\phi$) exhibits magnetically nonequivalent S-methylene protons.²¹ In a series of such ylides the nonequivalence is as high as 90 Hz.^{22,53}

The first X-ray structure of a crystalline sulfonium ylide has been reported.^{22,54} Dicyanomethylenedimethylsulfurane (1, $R_1=R_2=CN$, $R_3=R_4=CH_3$) was found to contain a pyramidal sulfur atom and a planar dicyanomethylene moiety. This suggested extensive charge delocalization of the carbanion since localized charge would have been characterized by a pyramidal arrangement of the carbon atom, *i.e.* it would then be isoelectronic with the nitrogen atom in ammonia. The observed dipole moment, 8.1D, was consistent with the highly polarized structure.

The basicity of phenacyl substituted sulfonium ylides can be correlated linearly with the Hammett σ -values.⁵⁰ From pKa studies Johnson and Amel found sulfonium salts to be more acidic than either phosphonium or arsonium salts.⁵⁵ This evidence supports the earlier work of Doering and Hoffmann⁸ which also suggested that the sulfonium group is more effective than either the phosphonium or arsonium group in providing delocalization for the carbanion of the resulting ylides. Although one cannot extrapolate thermodynamic stabilities from acidities, Johnson and Amel are justified in concluding that the sulfonium group stabilizes an α -carbanion to a greater extent. Furthermore, they found that replacement of a methyl with a phenyl group on sulfur decreases the pKa value by one unit and they interpreted this to mean that the inductive withdrawal effect of a phenyl group more than offsets its conjugative donation effect when attached to an 'onium atom.⁵⁵ Further support for this generalization obtains from recent pmr and ^{19}F -nmr evidence.³²

REACTIONS OF SULFUR YLIDES

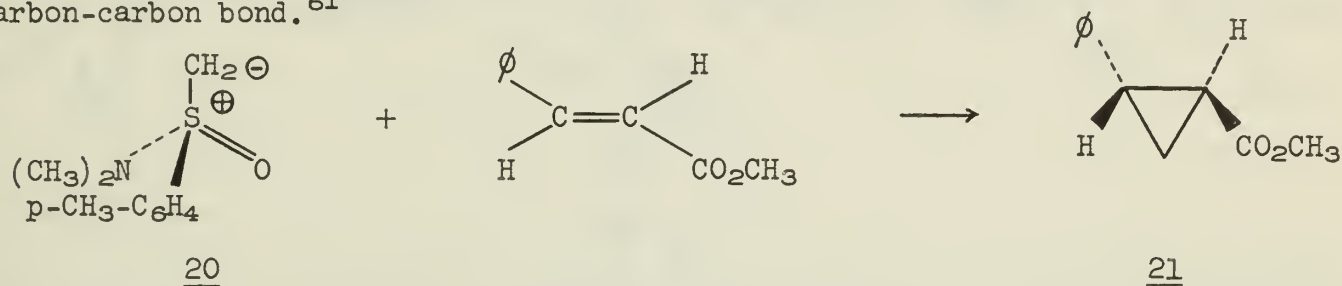
Since sulfur ylides are in fact stabilized carbanions, their reactions are exemplified by nucleophilic attack on a variety of unsaturated substrates as well as alkylation, acylation, and hydroboration. Thus reaction of sulfur ylides with carbonyl compounds, thiocarbonyl compounds, imines, and olefins produces oxiranes, episulfides, azirines, and cyclopropanes, respectively. An interesting example of such an addition is the first preparation of 1-azabicyclobutane (18).⁵⁶



The selectivity of sulfur ylides enhances their synthetic utility: methylenedimethylsulfurane (17) and methylenedimethyloxysulfurane (19) both transfer methylene to unsaturated centers, but with α,β -unsaturated ketones 17 adds exclusively to the carbonyl group while 19 undergoes a Michael addition to give the corresponding cyclopropyl ketone.^{1-5,57} With $\alpha,\beta,\gamma,\delta$ -unsaturated ketones 19 adds only to the γ,δ -carbon-carbon double bond.⁵⁸ The failure of sulfonium ylides to undergo the Wittig reaction is attributed to the greater strength of the P-O bond over the S-O bond and to the fact that phosphine oxides and sulfides are better leaving groups than phosphines and sulfoxides. It is of interest to note that arsonium ylides exhibit

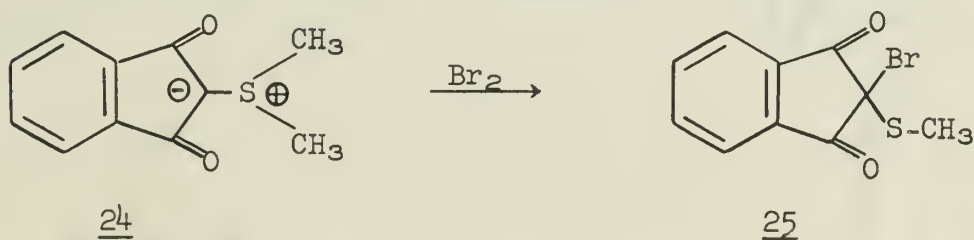
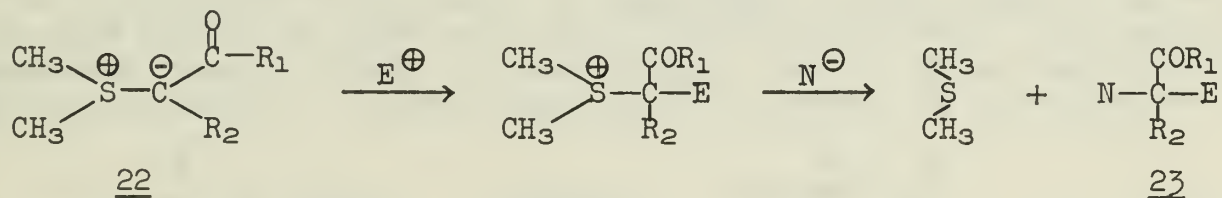
intermediate behavior producing both olefins and oxiranes upon treatment with carbonyl compounds.^{1a}

The chemistry of a new series of sulfoxonium ylides has been recently investigated by C. R. Johnson and his co-workers.^{59,60} They found that 20 and related derivatives provide a facile route to a large variety of Michael adducts and exhibit a remarkable stereospecificity: reaction of R-20 with trans-methyl cinnamate afforded 1(S),2(S)-(+)-trans-phenylcarbomethoxycyclopropane (21) with an optical purity of 30.4%.⁶¹ This novel asymmetric induction reflects a significant difference in activation energies leading to formation of the two possible betaine intermediates, presumably owing to their respective nonbonded and/or steric interactions. Since treatment of both dimethyl fumarate and dimethyl maleate with 20 produced optically active cyclopropanes with the same absolute configuration, it was concluded that the preferred betaine intermediate is sufficiently long-lived to allow for rotation about the carbon-carbon bond.⁶¹

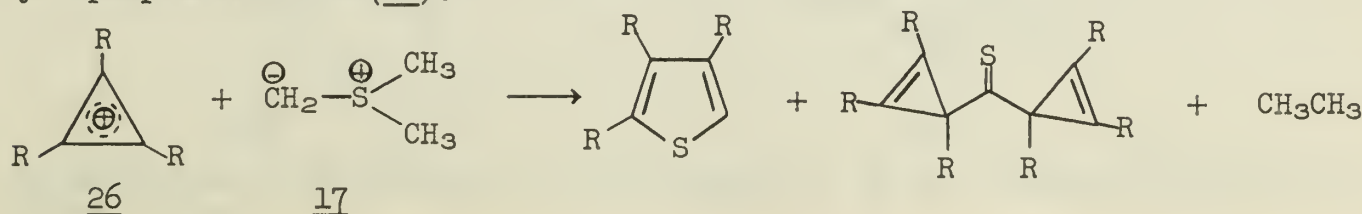


The reactions of a synthetically useful sulfoxonium ylide, carboethoxymethylene-dimethylsulfurane (22), have been investigated in a very thorough manner by Payne.⁶²⁻⁶⁵ Stable sulfur ylides were obtained in high yields by reaction of 22 with a wide spectrum of substrates.⁶⁵ Treatment of α,β -unsaturated compounds with 22 in aprotic media led to cyclopropane formation^{62,64} but in ethanol gave acyclic products of varying structure.⁶³

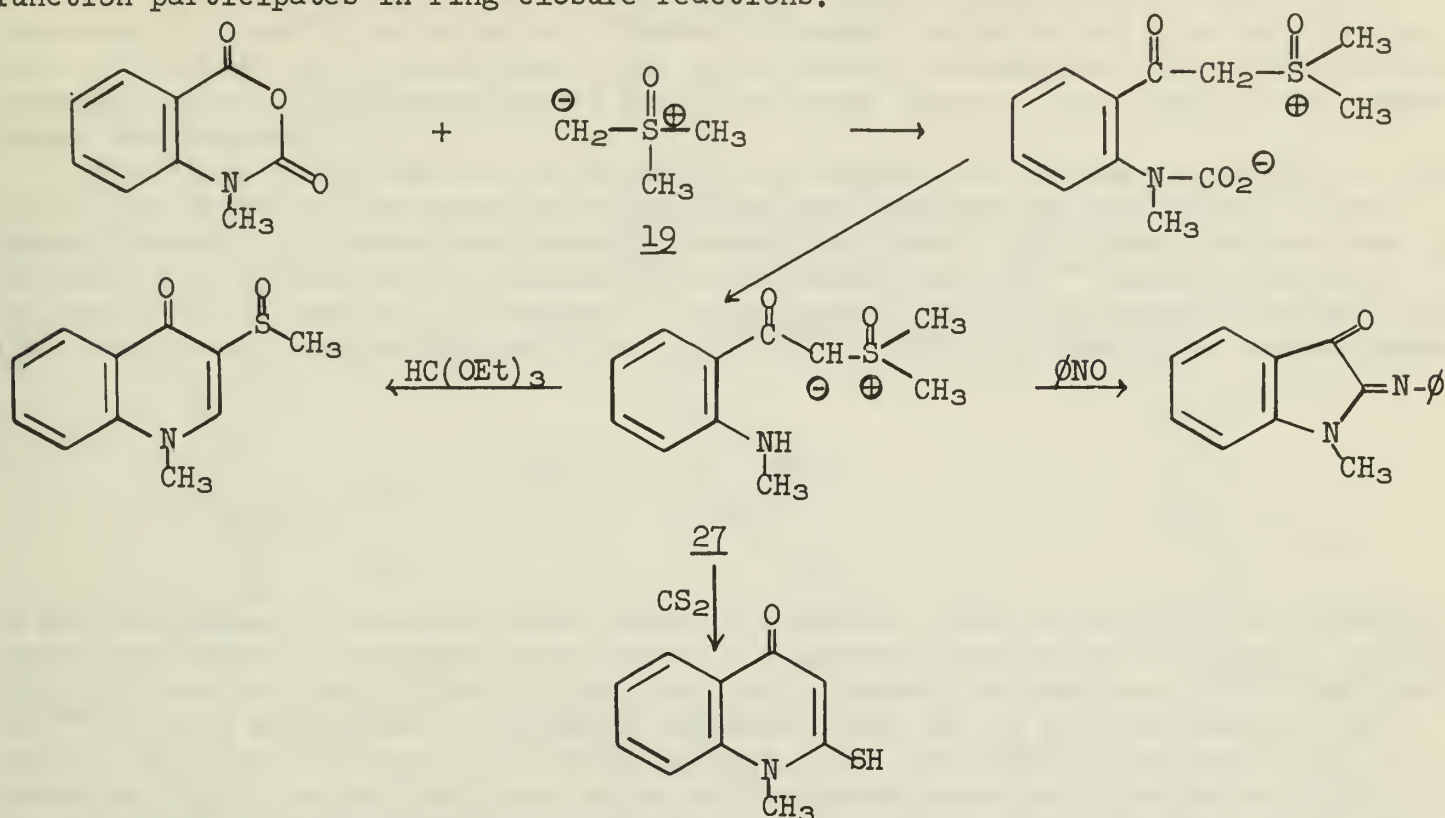
Hydroboration of sulfoxonium ylides gave the corresponding homologated alcohols upon oxidative work-up and was shown to be an effective route to alkylated esters and amides.^{66,67} Treatment of β -keto sulfur ylides (22) first with an electrophilic reagent (E) and then with a nucleophilic reagent (N) has been found to be a useful synthesis of α,α -disubstituted ketones (23).^{49,68,69} Similarly the reactions of 22 with bromine produced the corresponding α,α -dibromoketones in good yield.⁶⁹ Contrary to this behavior Moffatt has recently found that the very stable β,β' -diketo sulfoxonium ylide 24 reacted instantaneously with bromine giving quantitatively the bromomethyl sulfide 25, which could be hydrolyzed to ninhydrin.⁷⁰ This is a curious reaction of 24 since it is extremely inert toward the normal ylide substrates.



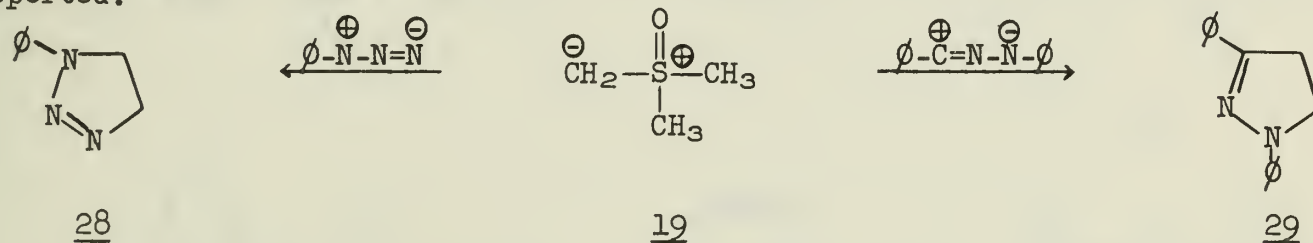
An interesting reaction has been discovered by Trost in the attack of 17 on cyclopropenium salts (26).⁷¹



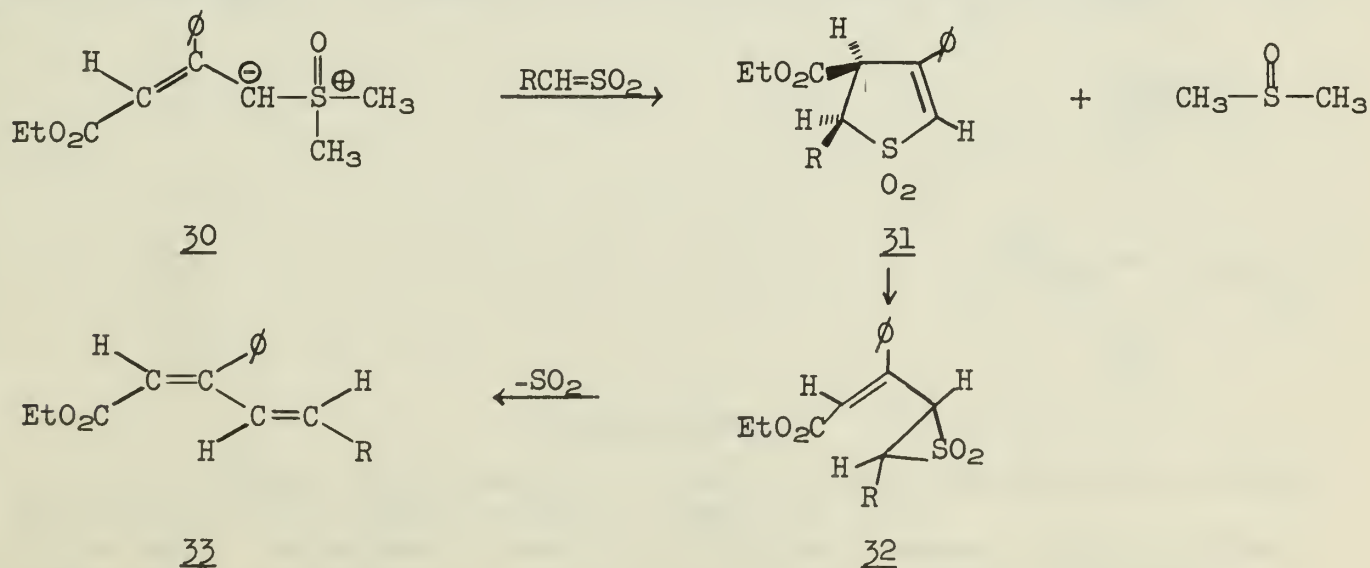
A new stable sulfur ylide (27) has been isolated by van Leusen and Taylor who found it to be a valuable heterocyclic intermediate since the ortho methylamino function participates in ring closure reactions.⁷²



Reactions of sulfur ylides with azides, nitrile oxides, nitrile imines, and diazo compounds gave an interesting variety of nitrogen heterocycles, e.g. 28 and 29,⁷³ and numerous other examples of additions to multiple bonds have been recently reported.⁷⁴⁻⁸³



The stereospecific production of trans,trans-1,3-dienes (33) from reaction of sulfoxonium ylides (30) with sulfenes (3) has been reported.⁸⁴ Ide postulated an intermediate betaine closing to episulfone 31; however, on the basis of orbital symmetry correlations⁴¹ it seems appropriate to propose the concerted $4\pi + 2\pi$

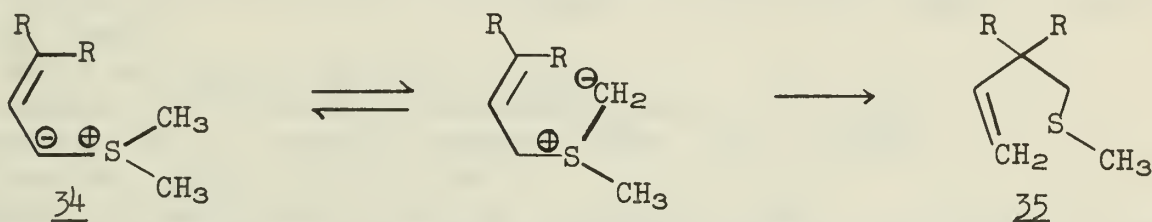


cycloaddition to 31 followed by rearrangement to 32 and subsequent expulsion of sulfur dioxide.

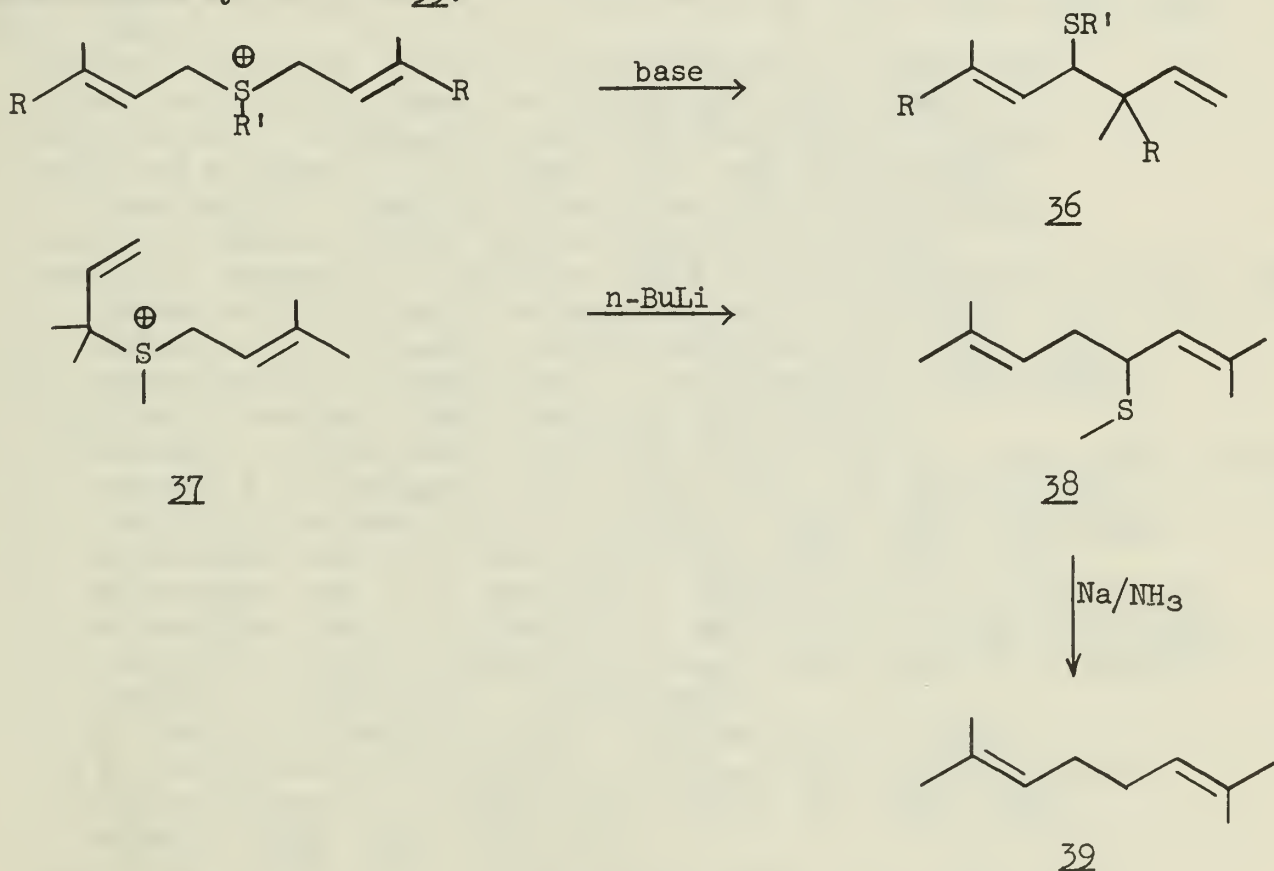
REARRANGEMENTS OF SULFUR YLIDES

The first known sulfur ylide, fluorenylidenedimethylsulfurane,⁸⁵ was found to rearrange to 1-methylthio-1-methylfluorene in ammonia solution at room temperature.⁸⁶ This transformation is analogous to the base-induced rearrangement of benzyl quaternary ammonium salts to ortho-substituted benzyl tertiary amines, also known as the Sommelet-Hauser rearrangement.⁸⁷

Previously sulfonium ions were thought to undergo the Stevens 1,2-shift in basic media, but Ratts and Yao have corrected Böhme and Krause's earlier report⁸⁸ that phenacyldimethylsulfurane gave α -methylphenacyl sulfide. They found instead that the rearrangement product was 1-(methylthio)-1-methoxystyrene,^{89,90} which is exactly analogous to the general electrocyclic rearrangement of allyldimethylsulfonium ylides (34) to allylcarbinyll methyl sulfides (35).^{23-25,91-99} This Cope-like rearrangement



is now recognized to contain broad predictive powers since it accounts for Sommelet-Hauser and Stevens rearrangement products, fragmentation products of certain cyclic ylides,⁹⁷ and may participate in the biogenetic pathway to squalene.^{98,99} The first test⁹⁶ of this biosynthetic mechanism suggested that the in vitro course did not involve the above electrocyclic rearrangement since the isomeric squalene type structure (36) obtains, but later evidence⁹⁹ substantiated the chemical validity of the proposed mechanism, i.e. base treatment of 37 affords 38 which was reduced to the squalene-like hydrocarbon 39.⁹⁹



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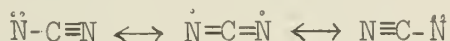
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CYANONITRENE CHEMISTRY

Reported by William H. Harned

September 30, 1968

Nitrenes are monovalent nitrogen compounds isoelectronic with carbenes. They may exist either as singlets with strongly electrophilic electron-deficient nitrogen or as triplet diradicals. Several reviews on nitrenes have appeared in the recent literature^{1,2} or in seminars.³⁻⁶ Cyanonitrene (NCN) was first encountered in 1960 by Jennings and Linnett,⁷ who observed it in the emission bands resulting from the reaction of active nitrogen with several hydrocarbons. Cyanonitrene may be depicted by the following resonance structures:



Cyanonitrene has been generated by reaction of active nitrogen with hydrocarbons⁷ or cyanide radicals,⁸ photolysis of fulminic acid,⁹ cyanogen,¹⁰ or diazomethane,¹¹ and photolytic (either in gas phase,¹² solution,¹³ or in a solid matrix¹⁴) and thermal¹⁵ fragmentation of cyanogen azide.

Herzberg and Travis¹¹ flash photolyzed a diazomethane:cyanogen:nitrogen mixture and observed a group of bands at 3290 Å. By isotopic substitution and analysis of the spectral data, the species under observation was shown to be NCN. Photolysis of cyanogen azide^{16,17} produced a species reported to be free NCN on the basis of the similarity of the absorption spectrum to that reported by Herzberg and by the well substantiated photodecomposition of azides by splitting off a molecule of nitrogen to form a nitrene.¹⁸ Evidence against a possible cyclic structure for NCN came from the failure to observe the expected ir absorptions for the skeletal modes which should be similar to those of diazarine.^{16,19} A linear structure is in agreement with the theory of Walsh.²⁰ The C-N bond distance for NCN, 1.232 Å, found by Herzberg agrees well with the distances, 1.20-1.22 Å, found for the C=N bonds in HNCO, HNCS, and CH₃NCS and is consistent with the bond formula N=C=N.

The electronic configuration for the ground state of NCN should be similar to that of CO₂ with the two most loosely bound electrons removed. The ground state and first two excited state configurations are:

Ground state KKK (1σ_g)² (1σ_u)² (2σ_g)² (2σ_u)² (1π_u)⁴ (1π_g)²
 First excited state----- (2σ_g)² (2σ_u)² (1π_u)³ (1π_g)³ 3Σ_g⁺, 3Σ_u⁺, 3Δ_u, 1Σ_u⁺, 1Σ_u⁻, 1Δ_u
 Second excited state----- (2σ_g)² (2σ_u) (1π_u)⁴ (1π_g)³ 3Π_u, 1Π_u

All three configurations should be linear.

Herzberg has assigned the 3290 Å absorption from flash photolysis of diazomethane to a 3Π_u ← 3Σ_g⁺ transition of NCN in the gas phase. From low pressure flash photolysis of N₃CN Kroto¹² and others²¹ have observed the 3Π_u ← 3Σ_g⁺ absorption and also a group of bands at 3327 Å, which, under high resolution and rotational analysis, were shown to belong to a 1Π_u ← 1Δ_g transition of NCN. It has been suggested that the primary process for photodecomposition of N₃CN is:



This is analogous to the photolysis of hydrazoic acid to give nitrogen and imidogen, NH (1Δ_g).⁴ Densitometer tracings show 1Π_u ← 1Δ_g absorption decreases in intensity with longer delay timer while 3Π_u ← 3Σ_g⁺ absorptions show an increase.

Cyanogen azide in cyclohexane shows two absorptions at 2750 Å (ε 103) and 2200 Å (ε 2175).²² Using a Pyrex filter to eliminate wavelengths below 2750 Å, no NCN (1Π_u ← 1Δ_g) absorption was observed from flash photolysis of a N₃CN:N₂ matrix whereas both singlet and triplet absorptions were observed from unfiltered gas phase flash photolysis. Milligan and Jacox^{17,23} and Schoen¹⁴ have proposed processes to account for the apparent spin-forbidden generation of triplet NCN.

In an effort to clarify the apparent difference in the multiplicity of NCN generated with and without a Pyrex filter, cyanogen azide was photolyzed at wavelengths controlled by various filters and the electronic multiplicity of the NCN generated was determined by the stereochemical course of insertion²⁴ into the tertiary C-H bonds of 1,2-dimethylcyclohexane (1).¹³ Solutions of N₃CN in cis-1 at

15° were irradiated using filters of Vycor (absolute cutoff point at $\sim 2120 \text{ \AA}$), Corex (absolute cutoff point at $\sim 2580 \text{ \AA}$), and Pyrex (absolute cutoff point at $\sim 2800 \text{ \AA}$). A fourth sample was thermolyzed at 50° . Results are shown in Table I.

Table I

NCN Conversion of cis-1,2-Dimethylcyclohexane to 1-N-Cyanamide Products

Reactn.	Conditions	% <u>cis</u> Insertion Product	% <u>trans</u> Insertion Product
1	$h\nu, \lambda > 2120 \text{ \AA}$	41	< 0.5
2	$h\nu, \lambda > 2580 \text{ \AA}$	39	< 0.5
3	$h\nu, \lambda > 2800 \text{ \AA}$	34	< 0.5
4	$\Delta, 50^\circ$	44	< 0.5

Gas liquid partition chromatography of the products of reactions 1-3 gave identical results. The indication from these data is that photolytically generated NCN inserts into tertiary C-H bonds stereospecifically regardless of the wavelength used in generation. Since only the singlet state should be involved in stereospecific insertion, whereas the triplet would insert in a stereorandom manner, all wavelengths used must produce only singlet NCN. This conclusion contradicts the work of Schoen¹⁴ and of Milligan and Jacox.¹⁷ Anastassiou and Shepalevy¹³ argue that irradiation through quartz should generate a highly vibrationally excited singlet NCN, which in a rigid matrix should undergo a relatively slow relaxation to a level where isoenergetic crossing to a $^3\Sigma_g^-$ potential surface could occur. Therefore the delay times of 30-200 μ sec between photoflash and analysis lamps are adequate for observation of the initially formed $^1\Delta_g$ state. Irradiation through Pyrex should produce NCN ($^1\Delta_g$) in a low vibrational level from which isoenergetic crossing to the $^3\Sigma_g^-$ state can occur rapidly. If under these conditions the lifetime of the $^1\Delta_g$ state is reduced below the minimum delay time employed (30 μ sec), the singlet could escape detection and the triplet appear to be the primary product. Insertion into tertiary C-H bonds must also occur before decay to the triplet ground state.

INSERTION²⁴ REACTIONS

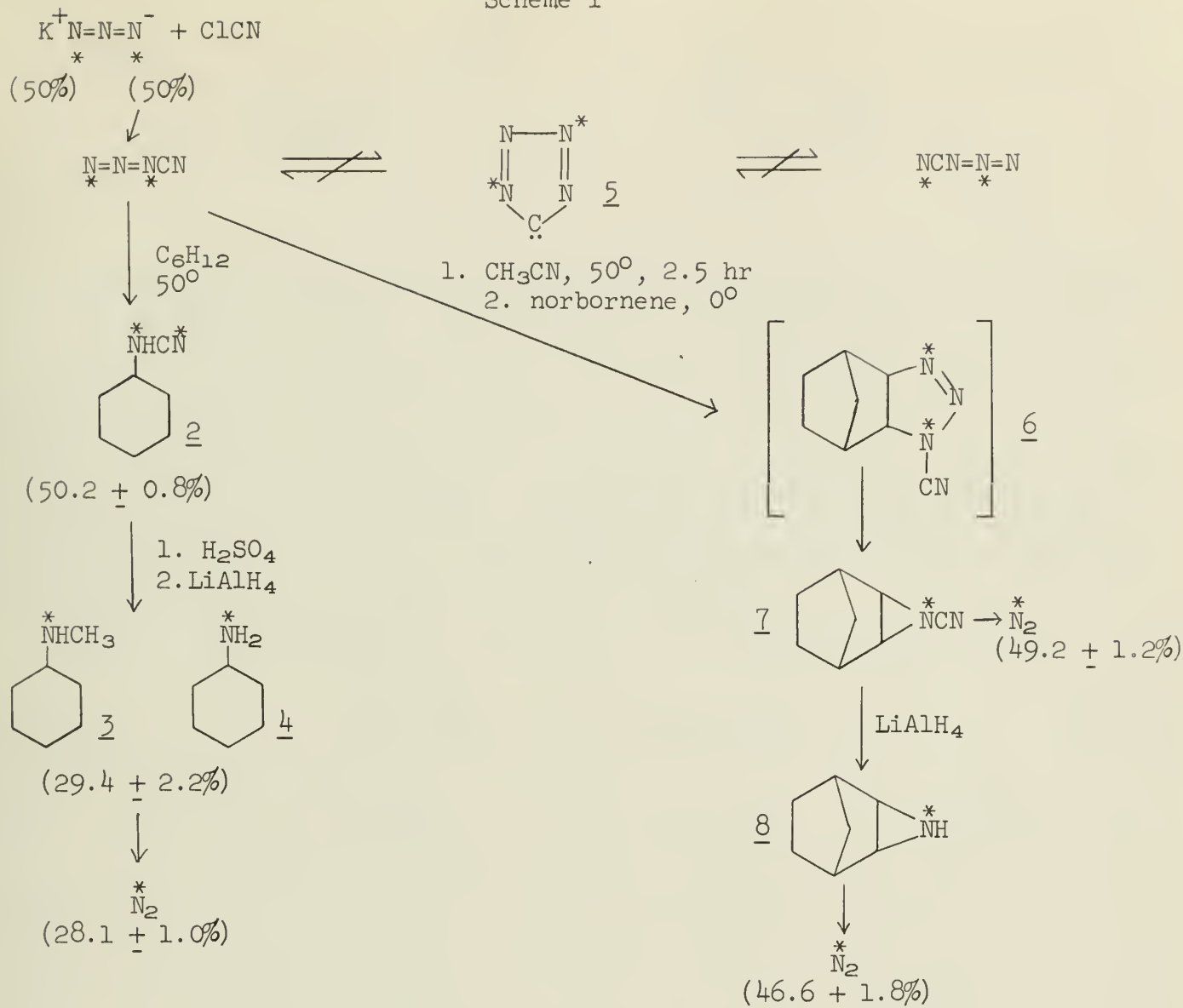
Cyanogen azide undergoes unimolecular fragmentation at $40-50^\circ$ to give NCN and molecular nitrogen. In paraffinic hydrocarbons, NCN inserts into the C-H bonds to form alkylcyanamides. To show that NCN is indeed an intermediate in the insertion reaction and that a mechanism involving direct reaction between cyanogen azide and the hydrocarbon is not taking place, Anastassiou and Simmons²⁵ caused appropriately labeled cyanogen azide to react with cyclohexane. Twenty-five per cent of the original ^{15}N label is expected in the degraded cyanamide resulting from an NCN intermediate with equivalent nitrogens. A control for the possibility of nitrogen scrambling in the azide prior to reaction was also run. The results are shown in Scheme I. (The per cent label shown refers to the per cent of the original ^{15}N label used in the potassium azide.)

If scrambling did occur in the azide, compound 8 should contain only half the amount of label found in 7. The intermediate triazole 6 could not be isolated and is probably destabilized by the electron-withdrawing cyano group. However, the identity of the amount of label in 7 and 8 precludes the possibility of scrambling at the N_3CN stage.

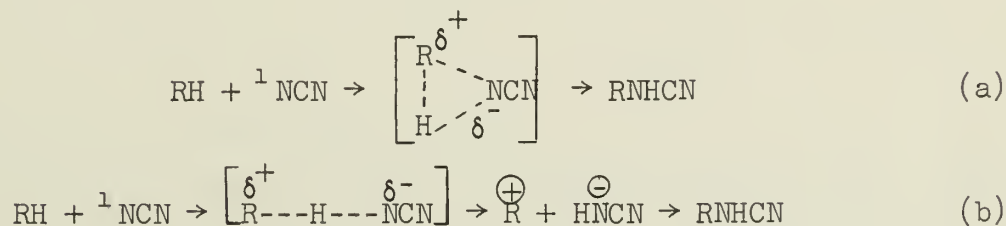
With the mild conditions used, $40-50^\circ$, NCN is most likely in a low energy electronic state, either $^3\Sigma_g^-$, $^1\Sigma_g$, or $^1\Delta_g$. Three distinct modes of insertion are possible.

Path (b) is expected only from the very highly electrophilic NCN ($^1\Delta_g$), in which there is a vacant low-energy bonding orbital. Path (a) ought to be stereospecific, leading to over-all retention of configuration, whereas paths (b) and (c) ought to give stereorandomly produced products. Thermolysis of N_3CN in cis- or trans-1 at 46.1° gave products (40% yield) which showed greater than 98% retention of configuration,

Scheme I



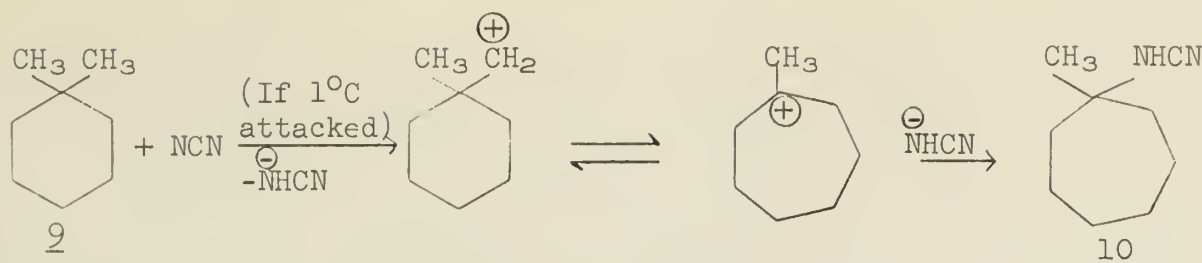
Scheme II



implying that reaction was by singlet via path (a). If path (b) is operative and a carbonium ion is formed, its presence should be apparent in intermolecular competition reactions between cyclooctane, cycloheptane, and cyclohexane. The cyclooctyl ring should be more reactive than the cycloheptyl ring, which in turn should be more reactive than the cyclohexyl ring if a carbonium ion is formed.²⁶ If path (a) or (c) is followed, little discrimination between various ring sizes



is expected.²⁷ Results are shown in Table II (B). All three carbocycles and n-hexane have nearly the same relative affinities. Also discounting the occurrence of any reaction via path (b) was the observation that thermolysis of cyanogen azide in 1,1-dimethylcyclohexane (9) produced no (i.e., < 2%) 1-cyanamido-1-methylcycloheptane (10). If abstraction of a methyl hydrogen of 9 formed a primary carbonium ion, the ion should undergo a Demjanov rearrangement to form 10.²⁹ This particular experiment, however, says nothing about tertiary C-H bonds, which should be more receptive to ion formation.



Selectivity of NCN insertion in the absence of solvent is shown by Table II (A). Thermally generated NCN appears to be slightly more selective than carbethoxynitrene generated by photolysis of ethyl azidoformate or by base-induced α -elimination of N-p-nitrobenzenesulfonyurethan, which in either case has a relative reactivity of approximately 1:10:30 for insertion into 1°, 2°, and 3° C-H bonds, respectively.²⁹ By contrast, dicyanocarbene shows no distinction in selectivity between primary and tertiary C-H bonds.³⁰

Since reaction with tertiary C-H is stereospecific (Reaction 4, Table I), path (a) in Scheme II is probably followed. Secondary and primary C-H bonds are less reactive and may permit singlet nitrene time to undergo intersystem crossing to the triplet state before reaction. Thus primary and secondary C-H bonds may react in the absence of solvent by paths (a) or (c) or both.

Table II.^a Reactivity of Cyanonitrene with Hydrocarbons at 46.1°

A			B		
Hydrocarbon	H	Affinity	Hydrocarbon	H	Affinity
	1°	1.0		2° (α)	1.62
	3°	67.0		2° (β)	1.30
	1°	1.0		2°	1.00
	2°	9.0			
	1°	1.0		2°	1.21
	2°	14.8			
				2°	1.2

^aValues are corrected for statistical factors.

In the preceding discussion, NCN was assumed to undergo insertion as a singlet before it could deactivate to the triplet ground state when nonstereospecific path (c) should become the predominant reaction mechanism. Singlet-triplet transitions can be induced by dilution with an inert solvent which increases the time between generation of the intermediate species and collision with a suitable substrate, by collisional vibrational deactivation to low vibrational levels of the first excited state where intersystem crossing to high vibrational levels of the ground state can occur, and by removal of spin forbiddenness through coupling of spin and orbital angular momentum. Anastassiou³¹ has thermolyzed cyanogen azide in cis- and trans- 1 without solvent and with various concentrations of CH₂Br₂, CH₂Cl₂, CH₃COOC₂H₅, and CH₃CN.

The expected course of reaction of cis- 1 with singlet and triplet NCN is shown in Scheme III, and the results are summarized in Table III. The thermal reaction run in CH₂Br₂ is seen to be stereochemically random, with the same mixture of stereoisomers produced regardless of the configuration of the starting hydrocarbon, while in CH₂Cl₂ the reaction remains partially stereospecific. These results were attributed to a "heavy atom" solvent effect, with NCN reacting as a triplet in CH₂Br₂ and as a mixture of singlets and triplets in CH₂Cl₂. This is in full accord with the theory³² that CH₂Br₂, containing the heavier halogen, should be more efficient than

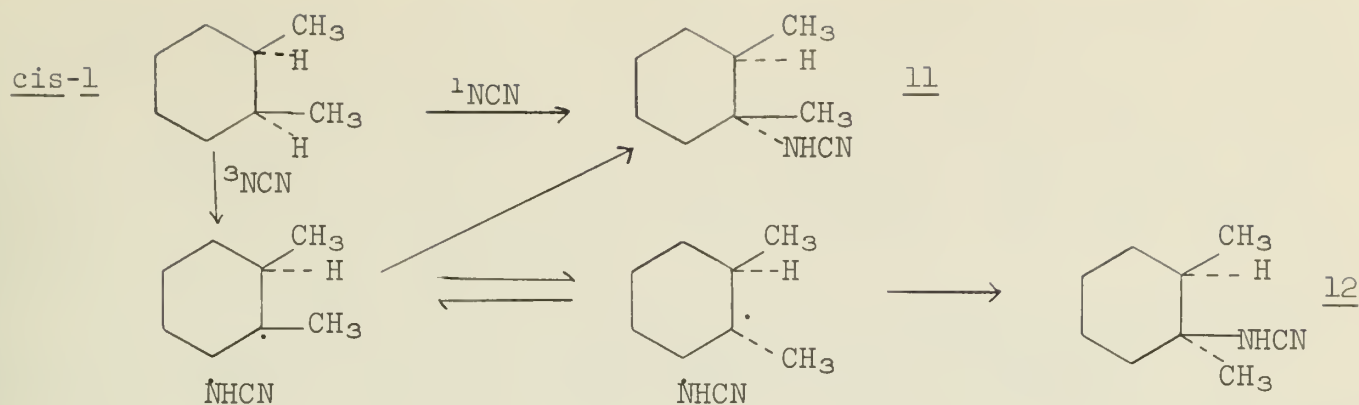
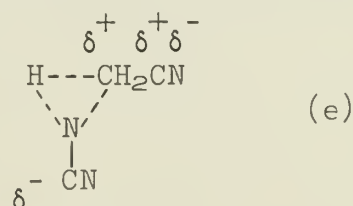
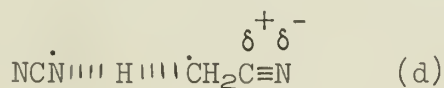


Table III. Stereochemistry of the Insertion of Cyanonitrene into the Tertiary C-H Bonds of cis- and trans-1,2-Dimethylcyclohexane as a Function of Solvent

Solvent	Concn, ^a %	Hydrocarbon	Temp, °C, +0.1	% <u>cis</u> - RNHCN <u>11</u>	% <u>trans</u> - RNHCN <u>12</u>	Over-all yield ^b %
None	100	<u>cis</u>	43.5	>98	<2	44
None	100	<u>trans</u>	43.5	<2	>98	46
CH ₂ Cl ₂	10	<u>cis</u>	41.0	75	25	26
CH ₂ Cl ₂	10	<u>trans</u>	41.0	36	64	32
CH ₂ Cl ₂	2	<u>cis</u>	41.0	62	38	34
CH ₂ Cl ₂	2	<u>trans</u>	41.0	39	61	23
CH ₂ Br ₂	10	<u>cis</u>	43.5	52	48	28
CH ₂ Br ₂	10	<u>trans</u>	43.5	52	48	26
CH ₂ Br ₂	10	<u>trans</u>	53.0	50	50	24
CH ₃ CN	10	<u>cis</u>	53.0	>98	<2	19
CH ₃ CN	10	<u>trans</u>	53.0	<2	>98	19
CH ₃ COOC ₂ H ₅	10	<u>cis</u>	53.0	53	47	21
CH ₃ COOC ₂ H ₅	10	<u>trans</u>	53.0	44	56	23
CH ₃ COOC ₂ H ₅	2	<u>cis</u>	53.0	52	48	11
CH ₃ COOC ₂ H ₅	2	<u>trans</u>	53.0	50	50	13

^aVolume per cent of hydrocarbon in solvent. ^bYield of a 1:1 mixture of amino- and methylamino-1,2-dimethylcyclohexanes, based on sodium azide.

CH₂Cl₂ in promoting singlet-triplet intersystem crossing, through coupling of spin and angular momentum. The spin-orbit coupling constants (ζ) for Cl and Br are 587 and 2460 cm⁻¹, respectively.³² By contrast, both CH₂Br₂ and CH₂Cl₂ ought to be equally effective in non-reactive collisional deactivation of singlet NCN, and neither should show a preference over the other for scavenging singlets or triplets from the solution.³¹ The complete stereospecificity observed with CH₃CN as the solvent (Table III) was explained by an efficient trapping of the less electrophilic NCN triplet by the electron deficient CH₃CN molecule. The hydrogen-abstraction-recombination mechanism of the triplet with CH₃CN (d) should be more favorable than the direct insertion mechanism of the singlet (e).



This, then, leaves the NCN singlet to attack the 1,2-dimethylcyclohexane. Moreover, CH₃CN does not contain a heavy atom and should be ineffective in promoting inter-system crossing except by collisional deactivation. The nearly total lack of stereospecificity seen with ethyl acetate cannot be attributed to any heavy atom solvent effect, nor can there be a process involving spin exchange between the solvent and

singlet NCN since the $T_1 \leftarrow S_0$ energy difference in ethyl acetate is larger than the $S_1 \rightarrow T_0$ energy difference in NCN.³¹ If a hydride-abstraction-recombination process between singlet NCN and the hydrocarbon occurs, it should be favored in the equally polar CH_3CN . However, CH_3CN shows no evidence for a two-step reaction, *i.e.*, no cis isomer from trans starting material. Anastassiou argues that the effect of ethyl acetate can originate from either or both of two processes. Ethyl acetate, containing more atoms than any of the other solvents employed, should be the more effective in collisionally deactivating an excited species. Also there could be a preferential scavenging of singlet NCN.

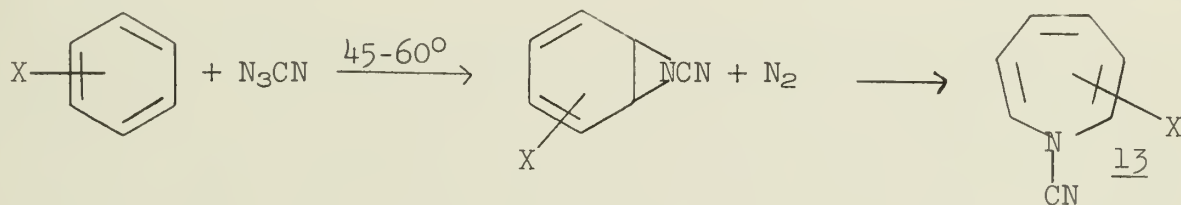
In view of the limited amount of data presented in Table III, no definite conclusion on the presence or absence of a heavy atom solvent effect can be drawn. The amount of reaction of NCN with primary and secondary C-H bonds of the hydrocarbon was not reported. The virtually complete absence of stereospecificity in ethyl acetate suggests that the observed results may in fact be due to some process not as yet elucidated.

Cowan and Drisko³³ have reported a heavy atom solvent effect in the photodimerization of acenaphthylene. However, other workers have failed to find any heavy atom effect on the photodimerization of ketones^{34,35} or on the addition of photolytically generated methylene to cyclohexene.³⁶ Pirkle and Koser³⁷ have found no singlet-triplet intersystem crossing attributable to a heavy atom solvent effect in the course of reaction of the carbene formed from photolysis of 3,5-di-*t*-butylbenzene-1,4-diazooxide. They have found that the carbene forms a halonium ylid with solvents containing a bromine atom. Possibly Anastassiou's work could be explained by invoking a mechanism involving a similar adduct formed by an electrophilic singlet nitrene attacking a bromine, oxygen, or chlorine atom of the solvent.



AZEPINE FORMATION

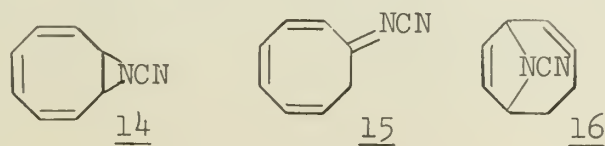
Cyanonitrene generated thermally from cyanogen azide gives N-cyanoazepines (13) in high yields ($\text{X} = \text{H}, \text{CH}_3, \text{p}-(\text{CH}_3)_2, \text{CO}_2\text{CH}_3, \text{Cl}, \text{F}, 6\text{F}, \text{CF}_3, \text{CCl}_3$).³⁸ The use of



¹⁵N labeled azide demonstrated that nitrene and not cyanogen azide is the attacking species. 7-Azanorcaradiene is presumed to be an intermediate in the reaction. All three possible isomeric N-cyanoazepines are obtained from reaction of the azide with monosubstituted benzenes. Electron-withdrawing substituents such as F, CCl_3 , or CF_3 appear to stabilize N-cyanoazepines, and there is less tendency toward rearrangement to phenyl cyanamides.

REACTION WITH OLEFINS

Nitrenes react with olefins in a manner analogous to that of carbenes, the singlet adding via a one-step concerted mechanism while the triplet adds by a two-step mechanism. Treatment of dilute cyclooctatetraene (COT) in ethyl acetate with cyanogen azide at 78°³⁹ did not yield any 1,2-adduct (14) but gave, in 30% total yield and in 68:32 ratio, two products which were shown by spectral and elemental analysis and by chemical conversion to known compounds to be N-cyano-1-iminocycloocta-2,4,6-triene (15) (major product) and N-cyano-9-azabicyclo[4.2.1]nona-2,4,7-triene (16) (minor product).



Compound 15 was shown³⁹ to be a product of a bimolecular reaction of cyanogen azide with COT. At room temperature COT and cyanogen azide gave exclusively 15 in 73% yield. Marsh and

Hermes²² have shown that cyanogen azide reacts rapidly with olefins at 0-35° to give alkylidene cyanamides and/or N-cyanoaziridines.

Compound 15 did not isomerize to the 1,4-adduct (16) at 78°. Since 16 was produced at 78° but not at temperatures below 40°, it must arise from reaction of NCN with COT or from rearrangement of a 1,2-adduct. Anastassiou has been able to characterize the 1,2-adduct, N-cyano-9-azabicyclo[6.1.0]nona-2,4,6-triene 14 from the nmr spectrum of a partially reacted mixture of azide and COT; however, 14 could not be isolated due to its thermal instability. The relative amounts of products 14:15:16 were found to be in a constant ratio (48:38:14), from 10% to 75% completion of reaction as indicated by evolved nitrogen. At longer reaction times the amount of 14 in the mixture decreased considerably. Compound 14 demonstrated no appreciable rearrangement to 15 or 16, as evidenced by heating known concentrations of 14, 15, and 16 for various times, with monitoring of the concentration changes by nmr using dimethyl phthalate as an internal reference. While 14 showed decreasing concentration with increasing time, the concentrations of 15 and 16 remained essentially constant.

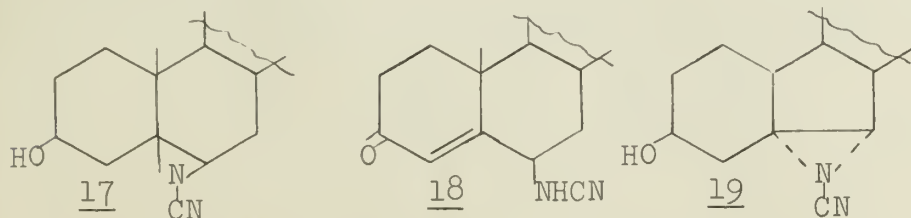
The 1,4-adduct 16 was viewed to result from a two-step process involving triplet NCN. The distance between the 1- and 4-carbon atoms in COT (2.8 Å) is probably too large for a concerted addition of singlet NCN. The 1,2-adduct, 14, was depicted to arise from singlet NCN,³⁹ although it is not clear why triplet NCN should not also be a major contributor to this product. In order to demonstrate whether or not multiplicity has any effect on product ratio, cyanogen azide and COT were brought together in solvents known³¹ to produce predominantly singlet or triplet NCN, i.e., CH₃CN, C₆H₁₂, CH₃COOC₂H₅, and CH₂Br₂. In CH₂Br₂, where exclusively triplet states are expected, the ratio 16:14 was highest and reached a maximum in the most dilute solution of COT. A similar effect was seen with ethyl acetate, except that the ratio 16:14 was smaller. A still lower 16:14 ratio was seen with CH₃CN and C₆H₁₂.

The 16:14 ratio increased with dilution in CH₂Br₂ and CH₃COOC₂H₅ but decreased with dilution in CH₃CN. This concentration effect was attributed to COT effectively competing with CH₃CN in scavenging triplet NCN. In support of this was the observation of an additional absorption in the nmr (τ 7.5-8) of the product mixtures obtained when CH₃CN was the solvent. The absorption showed an increase in intensity in the more dilute solution.

Solvent and dilution effects appear to be somewhat able to control product formation from COT but much less than in the case of tertiary C-H bonds of 1,2-dimethylcyclohexane (1). This difference was attributed to a greater affinity of both singlet and triplet NCN for addition to a double bond than for insertion into a C-H bond. From a competition reaction between COT and cyclohexane in a small amount of CH₃CN, the reactivity of a double bond in COT was found to be ca. 40 times that of the secondary C-H bond of cyclohexane and, from an indirect estimate, ca. 12 times as reactive as the tertiary C-H bond of trans-1.

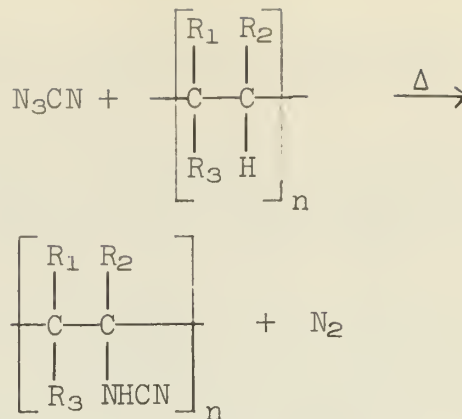
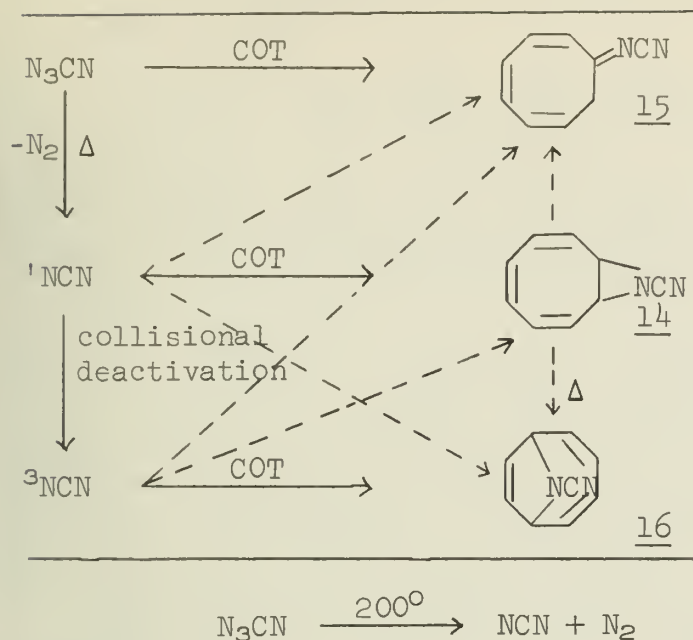
From the data obtained by Anastassiou, triplet NCN appears to prefer 1,4-addition, singlet NCN prefers 1,2-addition, and cyanogen azide gives the alkylidene derivative 15 exclusively. A very minor amount of rearrangement of 14 to 15 and 16 cannot be ruled out. Scheme IV summarizes the results. Full arrows represent predominant paths; dashed arrows represent minor or uncertain paths.

N-cyanoaziridines (17) have been obtained⁴⁰ from cyanogen azide and 3 β -hydroxy- Δ^5 -steroids at 50° and have been shown to possess the 5 β ,6 β configuration on the basis of their conversion to 6 β -(N-cyanamino)- Δ^4 -3-ketones (18). This reaction was considered to involve triplet NCN. Azacyclocholestanes (19) have also been obtained⁴⁰ in high yields.

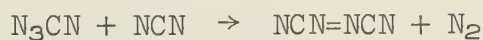
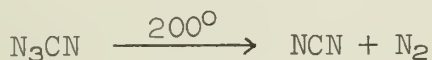


Cyanogen azide at 25-150° reacts with polymers⁴¹ containing at least one C-H bond and no C:C unsaturation, e.g., polyethylene, polypropylene, and poly-pivalolactone, to yield polymeric cyanamido products.

Scheme IV



Pyrolysis of cyanogen azide in the vapor phase produces the dimer of NCN , azodicarbonitrile (**20**) which will react instantly with dienes to form dicyanodiazacyclohexenes.⁴²



CONCLUSION

Cyanonitrile can be generated from cyanogen azide by photolysis or by heating above 40° . It reacts as a singlet or triplet. The relative amounts of singlet and triplet can be controlled by the use of appropriate solvents. Singlet NCN inserts stereospecifically into tertiary C-H bonds while the triplet inserts with random stereospecificity. Both triplet and singlet add to COT, with singlet giving preferred 1,2-addition and triplet giving preferred 1,4-addition. More work is required before a definite conclusion can be drawn concerning the mechanism of multiplicity control by solvents.

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RECENT ADVANCES IN THE CHEMISTRY OF PROTECTIVE GROUPS

Reported by D. R. Brittelli

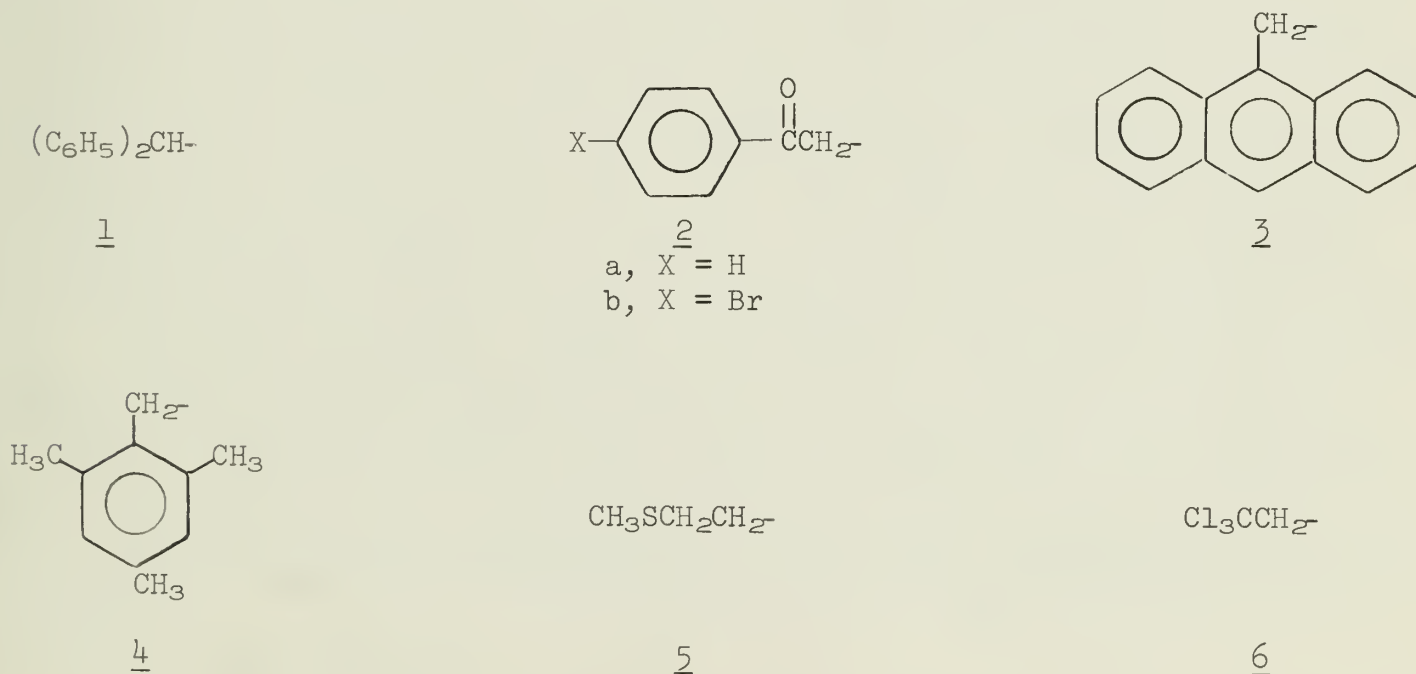
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INTRODUCTION

Protective groups are often necessary in order to carry out specific chemical transformations of multifunctional organic compounds selectively. Peptide chemistry, requiring the assemblage of long chains of chemically similar compounds with two and sometimes three functionalities, has long been an active area for the development of protecting groups. With the recent advances in the determination of the structures of many peptide natural products of increasingly greater complexity, there has been a concomitant need for even more mildly and selectively removed blocking groups for their synthesis. In response to this need, a whole host of new protective groups has been developed since the last literature review.¹ It is the goal of this seminar to summarize these recent methods. It is emphasized that, while most of these groups have been developed in the field of peptide chemistry, this in no way detracts from their general applicability, and special attention should be directed to the use of these protecting groups in the field of organic chemistry as a whole.

PROTECTION OF THE CARBOXYL GROUP

Historically, methyl and ethyl, *t*-butyl, and benzyl esters have been utilized as blocked carboxyl derivatives.¹ These groups are removed by saponification, mild acidolysis, and acidolysis or catalytic hydrogenolysis, respectively. Need has arisen, however, for a group more acid-sensitive than benzyl but less so than *t*-butyl or trityl (TRI),² which could be removed in the presence of the base-sensitive and catalyst-poisoning sulfur-containing amino acids.³ This requirement was met in the form of the benzhydryl (Bzh) residue (1).



N-Protected amino acid benzhydryl esters may be prepared from N-protected amino acids and diazodiphenylmethane, esterification with benzhydrol with the azeotropic removal of water, or reaction of the silver salt of the protected amino acid with benzhydryl chloride.² Alternatively, benzhydryl esters of amino acids themselves may be prepared from amino acid acid salts with non-nucleophilic counter-ions (typically the tosylates, perchlorates, or β -naphthalene sulfonates) and diazodiphenylmethane.⁴

Benzhydryl esters are cleaved by 0.2N hydrogen bromide in nitromethane (the preferred reagent) and also by catalytic hydrogenolysis, more strenuous acidic conditions, aqueous base, and by treatment with hydrazine, which results in formation

of the hydrazide.^{2,3,5} On the other hand, the Bzh residue is stable to 2N hydrogen chloride in organic solvents at room temperature, and thus its use is compatible with the use of amine protecting groups which are cleaved by the latter reagents.^{2,6}

Another pair of chemically similar recently developed carboxyl protecting groups are the phenacyl (PAC) (2a) and p-bromophenacyl (PAC(Br)) (2b) residues, which arose independently for use in peptide synthesis with carbobenzyloxy (Z) as the N-protecting group,⁷ but also as a carboxyl protecting group complementary to Bzh for use in blocking di-acids with the option of selectively uncovering either function.⁶ Both types of esters are synthesized by reaction of the amino acid with triethylamine and the corresponding phenacyl bromide and can be removed by hydrogenolysis or more selectively with sodium thiophenoxide.^{5,7} The esters are stable to the acidic conditions employed to remove the Bzh and Z groups and thus are compatible with the simultaneous use of these groups.^{5,7} The groups are labile enough, however, to necessitate the use of a rapid method of amidation in order for the protected peptide to be obtained in acceptable purity.⁷

A third set of acid-labile ester groups, 9-anthrylmethyl (AML) (3) and 2,4,6-trimethylbenzyl (TMB) (4), were also developed for use with Z as accompanying amino protection,^{8,9} and also to overcome the problem of the removal of protecting groups in the presence of catalyst-poisoning compounds. In addition, these acid-labile esters might be convenient for use in molecules in which hydrogen sensitive groups were being used for the protection of other functionalities.⁹ These esters can be removed under conditions sufficiently mild that Z is not cleaved and also by hydrogenolysis.¹⁰ The AML residue may also be removed by mild saponification. The esters are sufficiently acid stable that N-TRI and N-o-nitrophenylsulfenyl (NPS) can be selectively removed in their presence.¹¹

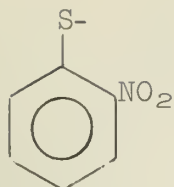
A new concept in deblocking methods has been introduced in the form of protective groups removable by means of β -elimination reactions, the β -methylthioethyl (MTE) (5)¹³ and the β,β,β -trichloroethyl (6) residues.¹⁴ MTE esters were designed to fill the need for an ester split off by mild alkaline conditions, and are prepared by esterification with azeotropic removal of water of a mixture of β -thiomethylethanol and the N-protected acid or by reaction with the chloride catalyzed by triethylamine.¹² The resulting MTE residue is stable to both acid and alkaline conditions; for removal, the β -protons of the group are activated to base attack by conversion into the methiodide or oxidation to the sulfone with hydrogen peroxide. Treatment with aqueous sodium hydroxide at pH 10 generates the free carboxyl and either dimethyl vinyl sulfonium iodide or methyl vinyl sulfone.^{12,13} The method fails with sulfur-containing compounds and the methiodide modification fails if the compound is otherwise susceptible to ready alkylation. The conditions used to oxidize the MTE group to the sulfone can also be used to effect simultaneously oxidative fission of a formyl amide. The group is generally compatible with the most common forms of N-protection.¹³

The β,β,β -trichloroethyl group has been used in a case where a mild reductive cleavage of the protecting group was desired.¹⁴ The esters have been prepared by the forced esterification method (water removed azeotropically) or by condensation of the alcohol with the N-protected acid through the agency of dicyclohexylcarbodiimide (DCC). Deblocking has been accomplished by reaction of the blocked derivative with zinc in acetic acid at room temperature for several hours. Although little has been published on the stabilities of these esters, they are apparently stable to mild acidic conditions.¹⁴

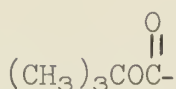
PROTECTION OF THE AMINO GROUP

In the past, the protective groups most commonly used for the protection of amino (with the most common methods employed for their removal in parenthesis) have been the formyl (mild acidolysis or oxidative cleavage with hydrogen peroxide), phthalyl (hydrazinolysis), tosyl (treatment with sodium in liquid ammonia), carbobenzyloxy (mild acidolysis or hydrogenolysis), t-butoxycarbonyl (mild acidolysis), trifluoroacetyl (mild basic hydrolysis), and trityl (mild acidolysis).¹

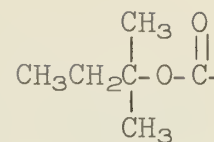
The most successful amine-protecting group to be developed recently has been the o-nitrophenylsulfenyl (NPS) (7) residue. The protecting group is introduced directly into the amine with o-nitrophenylsulfenyl chloride, and can be removed under a wide



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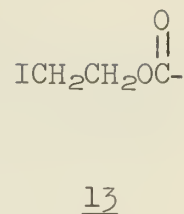
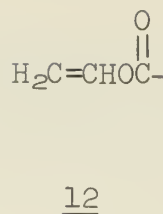
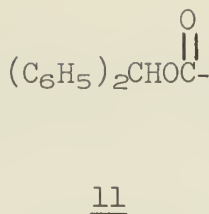
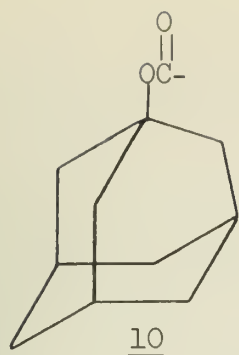
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variety of conditions. Exposure of the NPS-amine to two molar equivalents of hydrogen chloride in alcohol, ether, or most other common organic solvents cleaves the group quantitatively and selectively, even in the presence of groups as acid sensitive as t-butoxycarbonyl (BOC).¹⁵ In cases where the Z protecting group or sulfur-containing amino acids are not present, the group can be split off simply by passing the NPS-amine through a Raney nickel column.¹⁶ In cases where even the above mild acidic conditions are too strong or where a reactive heterocyclic aromatic nucleus might react with the o-nitrophenylsulfenyl chloride generated by the acidic cleavage, the NPS group is effectively cleaved in good yields through the agency of weakly acidic solutions of various good nucleophiles, the most effective of which were sodium thiosulfate,^{17,18} sodium iodide,¹⁷ sodium azide,¹⁷ benzenesulfonic acid imide,¹⁸ mercaptans (of which o-nitrothiophenol was the most conveniently used),¹⁹⁻²³ sodium cyanide,²⁰ sodium dithionite,¹⁷ and sodium bicarbonate.^{17,20} NPS can thus be removed without disturbing Z, benzyl, S-acyl, S- or N-TRI, t-butyl ethers, esters, or thioethers, BOC, N-acetoacetyl, alkyl esters, N-tosyl, trifluoroacetyl (TFA), and formyl residues.^{15,23} Care must be exercised in deblocking sulfur-containing compounds, however, as a nitrogen-to-sulfur NPS migration has been noted in cases where free sulfhydryl groups are present.^{5,24,25} No summary of conditions to which the NPS blocking group is stable has yet appeared in the literature. Apparently, it is removed by almost any acidic conditions, and a preliminary report indicates that it may be only marginally stable toward base as well.²⁰ It has already found great application as a very mildly cleaved acid-sensitive protecting group and has been utilized as the sole nitrogen protecting group in the synthesis of the octadecapeptide bradykinyl-bradykinin in 84% yield by the Merrifield solid state method.²³

One of the most effective amino protecting groups has been the BOC (8) residue.¹ Difficulties in the preparation of BOC amino acids exist because of the instability of t-butyl chlorocarbonate, however. Recent improvements in the synthesis of BOC amino acids have made use of t-butyl 2,4,5-trichlorophenyl²⁶ or pentachlorophenyl²⁷ carbonates as acylating agents. Another approach has been the use of BOC azide in pH controlled reactions with individual amino acids. The yields were maximized for each amino acid by controlling the pH, and data for the conditions giving maximum yields for 44 BOC amino acids have been compiled.²⁸ A new and more selective deblocking procedure with 98% formic acid has also been developed.²⁹ This has alleviated the problems of partial removal of Z from Z and BOC di-protected compounds and transesterification of benzyl esters prevalent in the older hydrogen chloride-in-methanol procedure.

To circumvent the instability of BOC chloride and still retain the convenience of the acid sensitivity of the protective group, attempts have been made to adapt other t-alkyl chlorocarbonates. The t-amyloxycarbonyl residue (AOC) (9) has been the most widely exploited. t-Amyl chlorocarbonate has been found to be stable, and the reagent gives yields superior to those in the BOC series.³⁰ Some problems with the formation of ureide-type by-products were noted in the preparation of some AOC amino acids, but these were solved by the use of the weaker base ethyl N,N-diethylglycinate in the place of triethylamine.³¹ Increased yields of the AOC method over the BOC method have been noted in the synthesis of a test hexapeptide,³² and preliminary results indicate that the t-amyl perchlorophenyl carbonate²⁷ and AOC azide³³ are also superior to the corresponding BOC compounds.

An even more stable chlorocarbonate is that derived from 1-adamantanol, used to introduce the adamantyloxycarbonyl (AdOC) grouping (10). This group was also designed to provide the convenience of having solid derivatives (some BOC amino acids are oils).³⁴ t-Adamantyloxycarbonyl chloride itself is a solid, and it does indeed

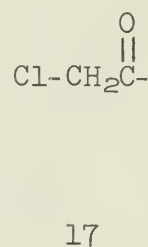
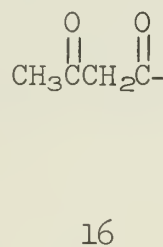
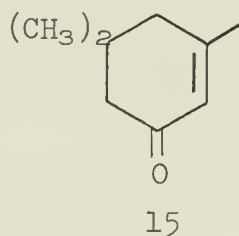
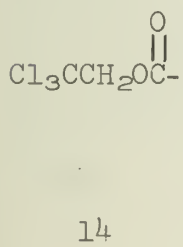


give nearly all solid AdOC amino acids. The yields of protected compounds suffer in comparison to those of the BOC and AOC series, however. The group is removed readily by treatment with trifluoroacetic acid at room temperature.

In the search for a protective group which could be removed by milder acidic conditions than those required to cleave the Z residue, the benzhydryloxycarbonyl (BhOC) (11) group was investigated.³ The group is introduced with BhOC azide and is cleaved by mild acidolysis, typically trifluoroacetic acid at 0° or hydrogen chloride in methanol, and also by hydrogenolysis. It is stable to hydrazinolysis, alkaline hydrolysis, and the acidic conditions useful in cleaving the NPS group.

Another promising new group is the vinyloxycarbonyl (VOC) (12) residue.³⁵ This protective group is introduced by reaction of the amine with the inexpensive and commercially available vinyl chloroformate under Schotten-Baumann conditions. The deblocking procedures consist of treating the protected amine with bromine in methanol (which liberates bromoacetaldehyde dimethyl acetal as a by-product), the same mild acidolysis used to effect cleavage of the BOC residue, or by treating with mercuric salts in acetic acid.

A number of groups have been introduced which are removed by non-hydrolytic procedures. The 2-iodoethoxycarbonyl (13) group was designed as a group removable by treatment with zinc in methanol under mild reductive conditions.³⁶ It was successful, but the derivatives thus formed were extremely toxic, and the corresponding bromo- or chloro- compounds were too unreactive to be useful. The β,β,β-trichloroethoxycarbonyl group (14) is sufficiently reactive and has been employed successfully, removal being effected by treatment with zinc powder in acetic acid at room temperature.¹⁴ Both groups are introduced by means of the corresponding acid chlorides.



The use of the 5,5-dimethyl-3-oxo-1-cyclohexanyl (DIM) (15) residue for the protection of amines in the form of vinylogous amides is promising. The protected derivative is prepared by reaction of the amine with dimedone.³⁷ The group is stable to hydrogenolytic conditions, sodium in liquid ammonia, and either acidic or basic hydrolysis. Removal is effected with either bromine (which liberates the amine along with 2,2-dibromo-5,5-dimethyl-1,3-cyclohexanedione) or, in the case of bromine-sensitive compounds, by treatment with nitrous acid, which produces the 2-oxime of 5,5-dimethyl-1,2,3-cyclohexanetrione as a by-product.³⁸ The group has already found special application in the Merrifield solid state method, where shorter chain peptide by-products can easily be separated before liberation of the desired product from its DIM protecting group, once the peptides have been liberated from the solid support. This was not possible previously, and conditions which detached the peptide from the resin invariably effected removal of the amine protecting group also, necessitating the separation of many chemically similar materials to achieve purification.³⁹ Another non-hydrolytic cleavage method is applied using the acetoacetyl (AA) (16) residue as a blocking group. The group is attached by reaction of the amine with diketene.⁴⁰ The resulting amide is stable to most commonly used acidic conditions.

The group is selectively removed by reaction of the derivative with phenylhydrazine, which liberates the free amine with production of 1-phenyl-3-methyl-5-pyrazolone as a by-product.

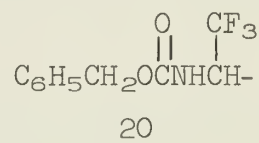
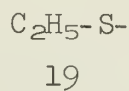
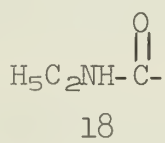
It has also been discovered recently that chloroacetyl (17) amides can be split by reaction with thiourea, giving pseudothiohydantion as a by-product.⁴¹ The use of this protecting group has previously been limited because of the severe conditions necessary to effect its removal, *i.e.*, either 10 *N* hydrochloric acid or boiling aqueous alkali.

PROTECTION OF THE SULFHYDRYL AND HYDROXYL GROUPS

Classically, benzyl (removed by treatment with sodium in liquid ammonia or by hydrogenolysis), TRI (cleaved by acid), tetrahydropyranyl (cleaved by mild acid), and Z have been used as blocking groups for sulfhydryl and hydroxyl groups.¹ The selectivity of removal allowed by these groups, especially in the case of the sulfhydryl derivatives, where it is often desirable to free selectively only two sulfhydryl linkages for oxidation into a disulfide bridge, was severely lacking. Accordingly, more elegant methods were sought. Introduction of the S-benzoyl (Bz) group, removed with sodium methoxide in methanol,⁵ and its use with the S-TRI (now removed selectively with mercuric acetate or silver nitrate) and Bzh (removed by acidolysis) groups allowed useful differentiations to be made. It was found that from a di-S-TRI-mono-S-Bzh peptide the two TRI groups could be selectively removed without disturbing the Bzh group and from a di-Bz-mono-TRI peptide the two Bz groups could be removed without disturbing the TRI residue.^{42,43} These transformations were carried out, moreover, without cleaving Z, methyl, ethyl, or *t*-butyl esters, BOC, N-TRI, phthalyl, or NPS groups in the same molecules.^{42,44}

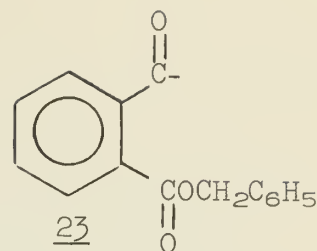
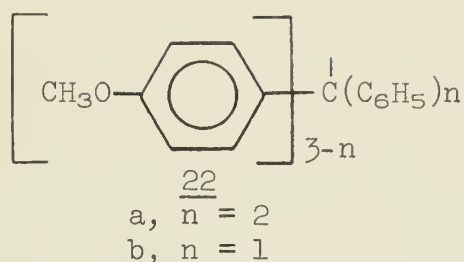
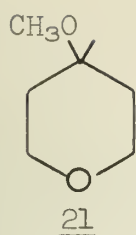
The facility with which S-acyl sulfhydryl compounds may be deblocked has led to another method for the synthesis of cysteine-containing peptides. L-serine^{45,46} or β -chloro-L-alanine⁴⁷ are substituted for L-cysteine in the synthesis of the peptide chain. These amino acids are then converted, either directly or as the corresponding tosylates, to the corresponding S-acetyl or S-benzoyl cysteines with thioacetic acid or potassium thiobenzoate, respectively. These derivatives are then deblocked in the usual manner.

New protecting groups recently introduced for the protection of sulfhydryl are S-ethylcarbamoyl (18),⁴⁸ applied with ethyl isocyanate, and S-ethylmercapto (19),⁴⁹ introduced by means of ethyl ethylthiosulfinate. The former group is stable to very strongly acidic conditions, but is readily removed by treatment with a variety of ammoniacal solutions. The latter group is stable to both strong acid and strong base reagents, and is rapidly cleaved by mercaptolysis with thiophenol or thioglycolic acid.



The 2,2,2-trifluoro-1-benzyloxycarbonyl-aminoethyl (Z-TF) (20) group has been applied to the protection of sulfhydryl,⁵⁰ hydroxyl,⁵¹ and the imidazolidinyl nitrogen of histidine.⁵² The group is introduced with either the corresponding chloride or 2,2,2-trifluoro-1-benzyloxycarbonyl-aminoethyl ethyl sulfone, and can be removed either by catalytic hydrogenolysis or by use of those mildly acidic conditions which serve to cleave the Z group. In the case of its protection of histidine, it is sufficiently electron-withdrawing to reduce the basicity of this amine to the point that it is no longer water soluble. The Z-TF group is stable to mild acidic or basic hydrolysis, but does contain an asymmetric center, so that the melting point and optical rotation of its derivatives are useless as checks on purity.

The tetrahydropyranyl (THP) group has enjoyed great popularity as a protecting group for hydroxyl. However, its use generates an additional asymmetric center in the molecule. When two THP groups are used in a compound already containing an asymmetric center, it is not possible to isolate a pure crystalline product. This disadvantage is eliminated by use of the 4-(4-methoxy tetrahydropyranyl) system (21).⁵³ The protecting group is introduced using 4-methoxy-5,6-dihydro-2H-pyran with a catalytic



amount of acid and can be removed by mild acidolysis.

The TRI group has found use as a hydroxyl protecting group, but in some instances was deemed too unreactive to mild acidolysis, and mono-*p*-methoxy (MMT) (22a) and di-*p*-methoxytrityl (DMT) (22b) groups were developed for hydroxyl protection in these cases.⁵⁴ Both groups are introduced by means of the corresponding trityl chloride, and are removed on standing in solution at pH 2.5 for several hours at room temperature. DMT derivatives are somewhat more acid-labile.⁵⁵ Conditions have now been developed so that MMT can be selectively applied to hydroxyl in the presence of amino groups.⁵⁶

Combining the properties of the phthalyl and Z groups has allowed the development of a new hydroxyl protecting group, the 2-benzoyloxycarbonyl-benzoyl ((2-Z)-Bz) residue (23).⁵⁷ The group is attached by reaction of the alcohol to be protected with the corresponding acid chloride, and is readily removed by hydrogenolysis to remove the benzyl group followed by hydrazinolysis to liberate the alcohol.

PROTECTION OF THE GUANYL GROUP

The guanyl moiety of arginine has long been difficult to protect satisfactorily. The desired protecting group should be a strong enough electron sink to reduce the basicity of the guanyl sidechain, but still must be able to be removed completely. Of the groups in the literature, only nitro and tosyl satisfy the first requirement. Recent developments in this area have concentrated on finding methods to remove these two residues completely. Recent work involving the electrolytic reduction of nitro, arylacyl, and sulfonyl groups suggested that this method might be applicable to the deblocking of arginine derivatives. Indeed, nitro⁵⁸ and tosyl⁵⁹ were both successfully removed by this procedure. However, in the former case prolonged reduction (with concomitant side reactions) was necessary, and in the latter the product must be separated from copious quantities of the electrolyte, tetraethyl ammonium chloride. This difficulty has been overcome, and the nitro group, removed reductively by treatment with zinc and hydrochloric acid, is the protective group of choice for arginine guanyl at present.⁵⁹

SUMMARY

With the advent of the recent increase in the number of well-developed protecting groups, the organic chemist now has at his disposal a whole spectrum of blocking groups from which to choose. Many problems still remain unsolved, however. Lack of space has prevented the description of every new suggestion which has appeared in the literature, but the more successful and widely applicable have been presented. Although the groups discussed in this seminar appear promising, only the test of time and further use will allow the utility of this new generation of protecting groups to be evaluated.

Table I represents a compilation of the removal conditions and stabilities of commonly used protective groups and those newer reagents discussed in this seminar. Included in the sets of conditions commonly used to deblock protected compounds are those of two new recently developed methods, electrolytic reduction of aryl amides and esters⁶⁰ and cleavage with anhydrous liquid hydrogen fluoride,⁶¹ a method which effectively removes nearly everything except tosyl and simple alkyl residues.

TABLE I

S-ethyl carbamoyl	S	S	S	<u>C</u>	<u>C</u>	<u>C</u>	C	S				C
N ^G -tosyl	S	S	S				C				S	<u>C</u>
N ^G -nitro	S	S	S	S	S				C		C	<u>C</u>
Mono-, dimethoxytrityl	C	C	C	C	C	C	S			C		
4-(4-methoxy THP)	C	C	C	C	C	C	S			C		
S-benzhydryl									S	S	S	<u>C</u>
S-trityl									S	S	<u>C</u>	S
S-benzoyl	S			S					S		S	<u>C</u>
DIM						S	S	S	S		<u>C</u>	
Vinyloxy carbonyl	C	C	C	C	<u>C</u>	C		R			<u>C</u>	<u>C</u>
Benzhydryloxy carbonyl	C	C	C	C	C	S	S	S	C	S		
Cl ₃ CCH ₂ O ₂ C-, ICH ₂ CH ₂ O ₂ C-					S		R				<u>C</u>	
<u>o</u> -nitrophenylsulfenyl										<u>C</u>	<u>C</u>	M
β,β,β-trichloroethyl				S							<u>C</u>	
trimethylbenzyl	<u>C</u>			<u>C</u>						S		
9-anthrylmethyl	<u>C</u>					<u>C</u>		C				
phenacyl, PAC (Br)	S	S		S				<u>C</u>		S	<u>C</u>	
benzhydryl ester	C	C	S	C	<u>C</u>	S	C	C	C	R	<u>C</u>	
benzyl ester	M	S	R	C	S	S	C	<u>C</u>	C	S		C
<u>t</u> -butyl ester	C	C	<u>C</u>	C	<u>C</u>	S	M	S	S	R	S	C
methyl, ethyl ester	S	M	S	<u>C</u>	S	S	<u>C</u>	C	S	R	S	S
S,N,O-benzyl	S		S		S	S	S	C	<u>C</u>	S	S	<u>C</u>
N-trityl	S		<u>C</u>	C	<u>C</u>	<u>C</u>	S	S	C		S	C
BOC, AOC, AdOC	C	C	<u>C</u>	C	<u>C</u>	S	S	S	S	S	S	C
Carbobenzoxy and Z-TF	<u>C</u>	C	M	<u>C</u>	S	S	S	S	<u>C</u>	C	S	S
Tosyl	S	C	S	S	S	S	S	S	<u>C</u>	S		C
Phthalyl	S		S	S	S	S	R	R	S	R	<u>C</u>	C
Trifluoroacetyl				C	S	S	C	C	S	R		S
Formyl	S		<u>C</u>	C	S	S	S	S	S			S

KEY

S stable

M of marginal stability

C cleavable

R side reaction

C method of choice for
removal of this groupN^G on guanido nitrogen

HBr, acetic acid, RT, 30 min.

HBr, acetic acid, 60°, 1 hr.

HCl, ethanol, 2 da., RT

10N HCl, acetone, 1 hr., 100°

CF₃COOH, 30 min., RT

Acetic acid, 100°, 10 min.

KOH, ethanol-water, 2 hr., RT

NH₄OH, 30 min., RT

Hydrogen, Pd on charcoal

Sodium in liquid ammonia

NH₂NH₂, methanol, 2 hr., 60°0.2N HBr, CH₃NO₂, 30 min., RT

Mercaptan, 30 min., RT

Zn, acetic acid, 2.5 hr., RT

Bromine or nitrous acid, RT

Mercuric ion, 30 min., RT

Anhydrous HF, 0°, 60 min.

CH₃ONa, methanol, RT, 15 min.

Electrolytic reduction

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CONFORMATION STUDIES OF EPHEDRINE ISOMERS

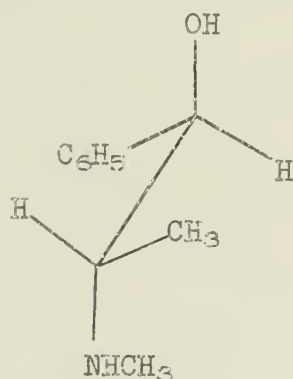
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October 31, 1968

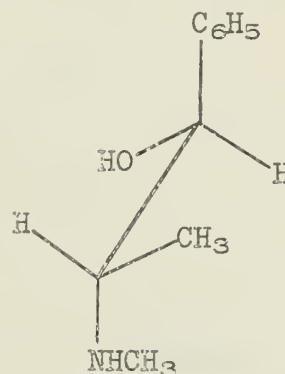
INTRODUCTION

In 1887, Nagai isolated ephedrine, the active principle of "Ma-Huang" (*Ephedra vulgaris*),¹ an herb used medicinally by the Chinese for thousands of years.^{2,3} While the drug was initially of interest as a mydriatic, an enormous literature has accumulated on its uses and chemistry since Chen and Schmidt^{4,5} called attention to its therapeutic possibilities, particularly with respect to its pharmacological similarity to epinephrine.

Attempts at the synthesis of ephedrine or ephedrine-like substances were reported as early as 1904, but it was not until 1920 that Eberhard⁶⁻⁸ and Späth and Göhring⁹ obtained what are now recognized as the optically inactive forms of ephedrine and its diastereomer, ψ -ephedrine. Establishment of the primary structure of ephedrine and ψ -ephedrine then permitted an investigation of the configuration of the natural products. Emde¹⁰⁻¹⁵ established, by interconversion of the two materials and by reduction of each to the common product (+)-deoxyephedrine, that the naturally occurring materials differed only in configuration at C_O.



1
(-)-ephedrine



2
(+)- ψ -ephedrine

Freundenberg^{16,17} and Leithe¹⁸ were able to correlate the configuration about C_O with mandelic acid. Freundenberg¹⁹ also correlated the configuration about C_N with alanine. The configurations of the four diastereomers are summarized in modern nomenclature in Table I.

Table I²⁰ Configuration of the Ephedrines

	C ₆ H ₅ CH(OH)CH(NHCH ₃)CH ₃		
	<u>1</u>	<u>2</u>	
(+)- ψ -ephedrine	1S:2S	(-)-ephedrine	1R:2S
(-)- ψ -ephedrine	1R:1R	(+)-ephedrine	1S:2R

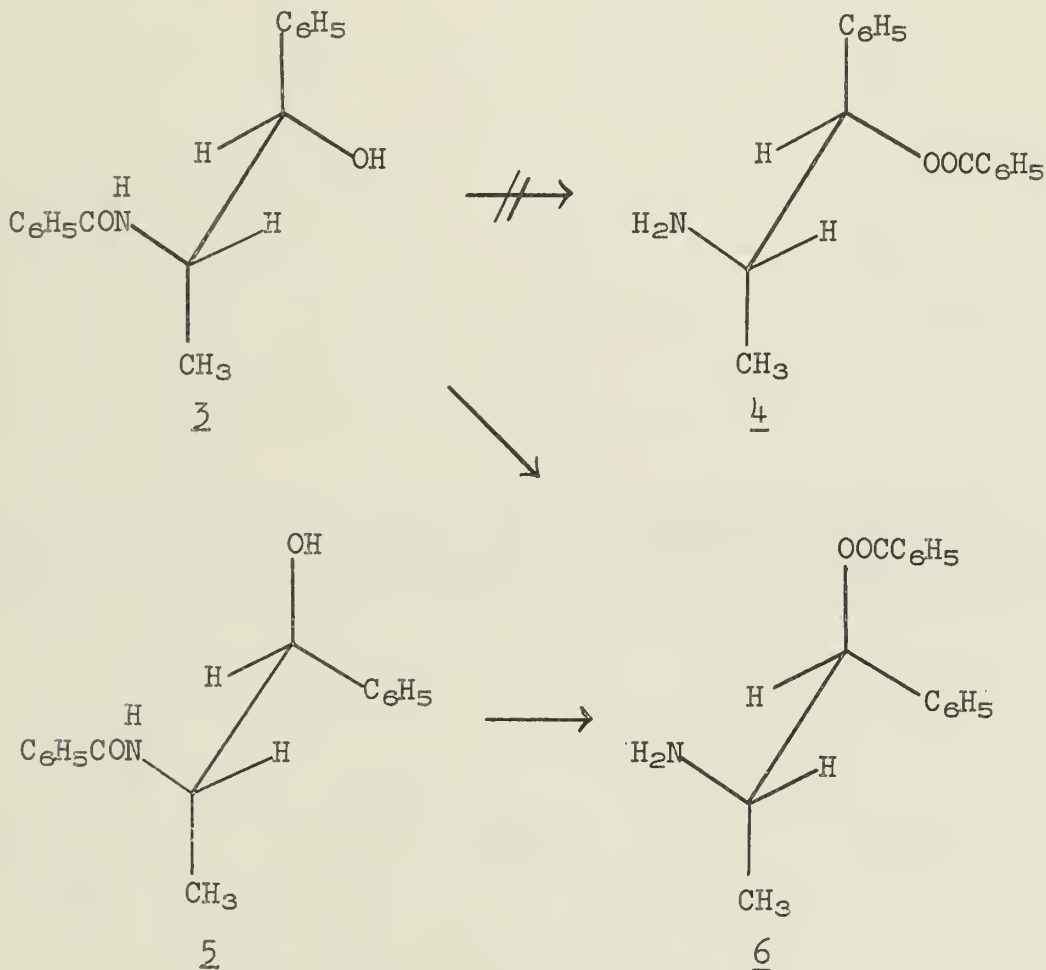
CONFORMATION STUDIES BASED ON CHEMICAL PRINCIPLES

The earliest suggestions concerning what we now denote "conformation" were made, in the ephedrine case, by Späth and Göhring,⁹ by Emde,¹⁰ and by Nagai and Kanao,²¹ all of whom felt that ephedrine and ψ -ephedrine must certainly reside in different conformations since there were marked differences in reactivity. It had been noted that ephedrine formed a hydrate, while ψ -ephedrine did not. Emde explained this difference in behavior, as well as the much higher melting point of the ψ -ephedrine base, as due to "eine intramolekulare basisartige Absättigung der Restvalenzen der OH- und NHCH₃-Gruppe im Pseudo-ephedrin" which would not permit the formation of a hydrate.

Freundenberg and coworkers,¹⁶ in a study of the configuration of ephedrine, indicated that all studies of the "configurational relationship" of ephedrine and ψ -ephedrine based on the hypothesis that in one of the isomers the OH and NHCH₃ groups were closer together than in the other must be invalid since the C_O-C_N bond was free to rotate.

Fodor and his coworkers^{22,23} reviewed the earlier work in 1949 and expressed their belief that the molecule was not free to rotate as Freundenberg had indicated. They interpreted the preferential formation of a hydrate by ephedrine as being due to the presence of a "hydrogen bridge" in that molecule which could not be formed by ψ -ephedrine due to a different relative orientation of the OH and NHCH₃ groups.

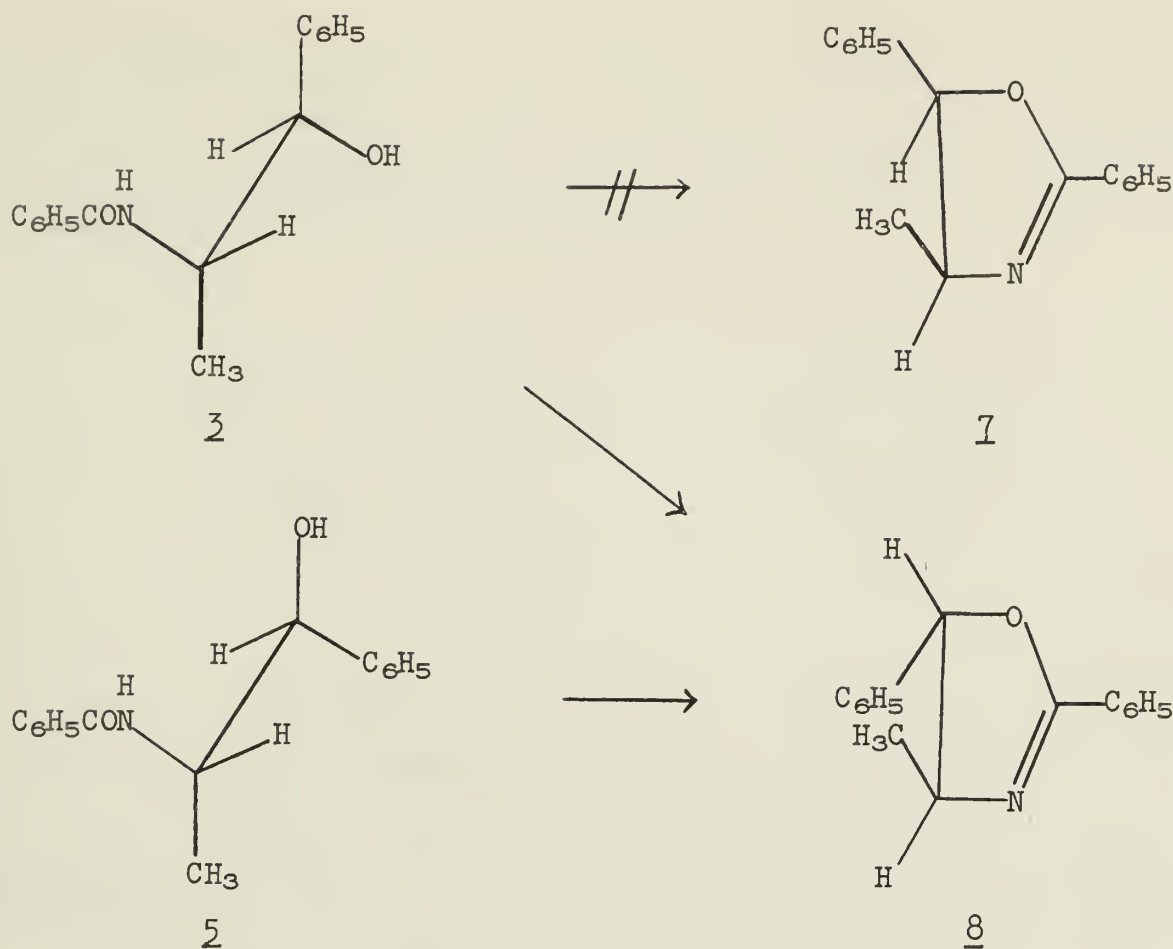
Fodor and coworkers prepared N-benzoyl-(+)-nor-ephedrine (3) and N-benzoyl-(+)-nor- ψ -ephedrine (5). Each compound was then treated with alcoholic hydrogen chloride at room temperature. In the nor-ephedrine case starting material was recovered along



with varying amounts of O-benzoyl(+)-nor- ψ -ephedrine (6), depending upon the exact reaction conditions. In the nor- ψ -ephedrine case, only compound 6 was obtained. The authors chose to explain this on the basis of an initial inversion of compound 3 to yield the appropriate nor- ψ -ephedrine isomer which would then undergo the normal acyl migration. This inversion could, presumably, occur by formation of a carbonium ion at C_O. Configurational equilibration at that center would then yield starting material plus the reactive inversion product which would then be converted to 6.

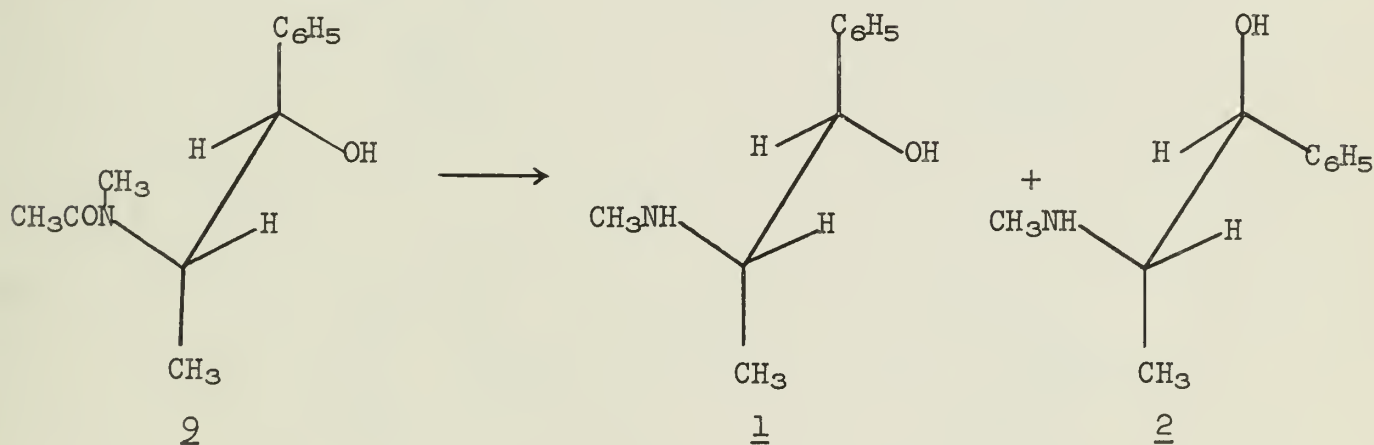
Similarly, treatment of compounds 3 and 5 with cold thionyl chloride yielded in each case the oxazoline salt corresponding to ψ -ephedrine (8). Again, the authors chose to explain these results by an initial inversion of 3 to yield the corresponding isomer in the ψ -ephedrine series.

The overall difference in mechanism was felt to have been induced by restricted rotation about the C_O-C_N bond which yielded molecules in which the NHC(=O)R and OH groups were more often cis (syn) in acyl-nor- ψ -ephedrines and more often trans (anti) in acyl-nor-ephedrines. This, Fodor reasoned, would force the NHC(=O)R and OH groups in the ephedrine series to assume a position of proximity either by

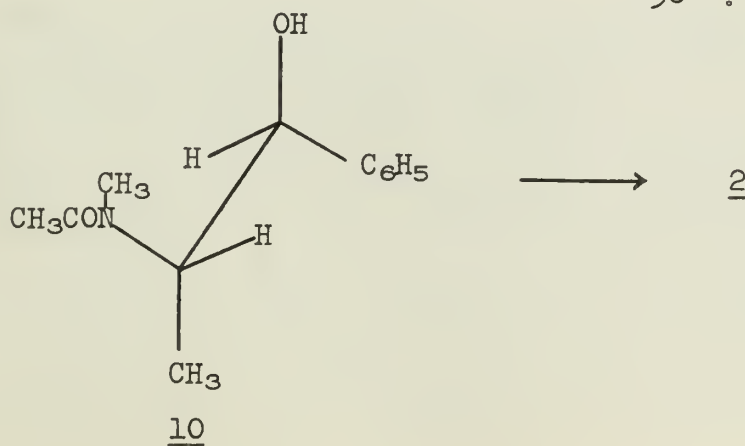


inversion or rotation, the former apparently being the lower energy process.

Welsh^{24,25} described the treatment of N-acetyl-(-)-ephedrine (9) and N-acetyl-(+)- Ψ -ephedrine (10) with hot 5% hydrochloric acid. Treatment of 9 in this fashion

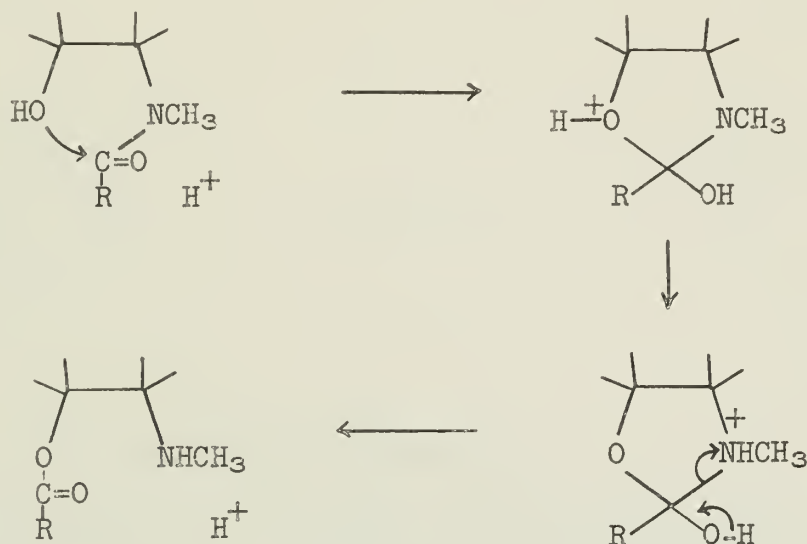


38 : 62

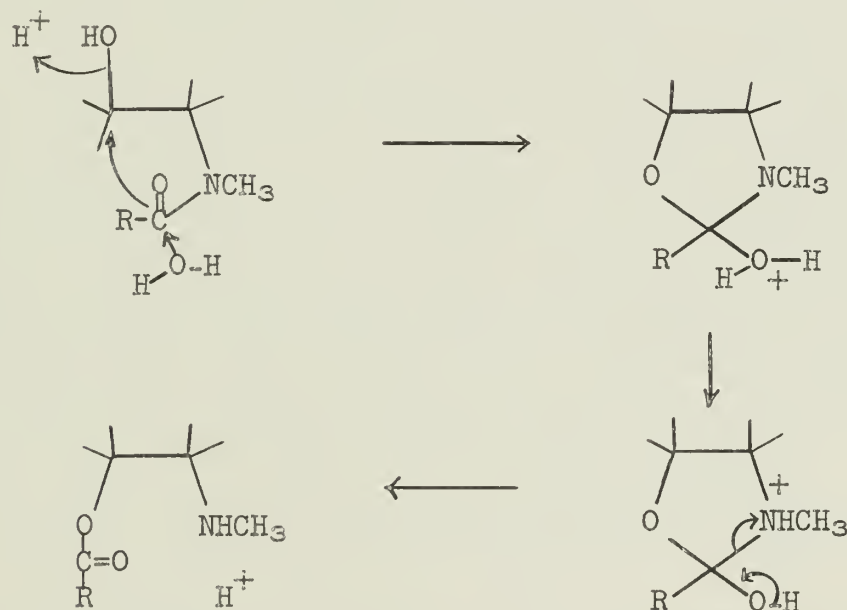


gave a 38:62 mixture of (-)-ephedrine (1) and (+)- Ψ -ephedrine (2) in quantitative yield, while treatment of N-acetyl-(+)- Ψ -ephedrine in the same manner gave only (+)- Ψ -ephedrine. Welsh²⁴ initially attributed this difference to inversion of 2 prior to acyl migration. A control experiment, however, indicated that (-)-ephedrine itself was stable to hot 5% hydrochloric acid.²⁵ This pointed to different mechanisms for the formation of compounds 1 and 2 from 2 and, on this basis, Welsh proposed a retention mechanism and an inversion mechanism.

Retention Mechanism:

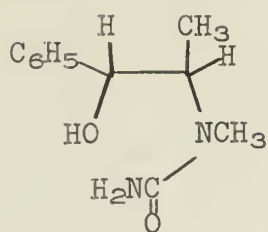


Inversion Mechanism:

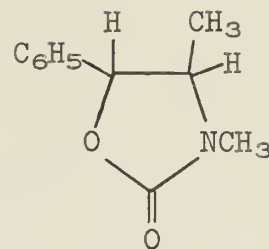


From the evidence that he had gathered, Welsh concluded that there must be "differences in spatial arrangements of the groups in the diastereomers" to allow them to proceed along different reaction pathways.

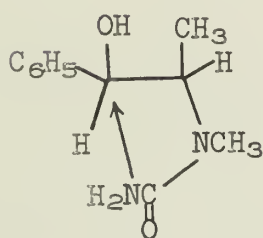
The hypothesis that ephedrine and Ψ -ephedrine resided in different conformations was supported further by Close²⁶ through a study of the fusion reactions of the compounds with urea. At the reaction temperature (170-210°) urea was converted to cyanic acid, which attacked the amine to give compound 11 from Ψ -ephedrine and compound 13 from ephedrine. These compounds were then condensed to oxazolidone 12 and imidazolidone 14, respectively. Close reasoned that the difference in mechanism was due to the difference in proximity of the terminal amino group to the hydroxyl group. Where approach was easy, the oxazolidone was formed; where approach was difficult, a rearward attack on C_O occurred by an S_N2 mechanism, resulting in expulsion of the hydroxyl group.



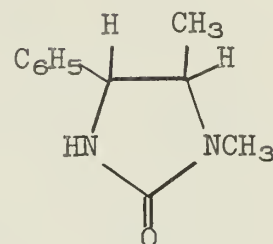
11



12



13



14

CONFORMATION STUDIES BASED ON PHYSICAL PRINCIPLES

In 1954, Phillips reported the X-ray crystallographic data on the ephedrine and Ψ -ephedrine hydrochlorides.²⁷ He indicated that the OH and NHCH₃ groups were very close together (3.0 Å between the O and N atoms), but that this might be due to constraint of these two groups through bonding to the chlorine in the crystal lattice and that the same geometry would not necessarily be found in crystalline ephedrine itself. He did not study directly the position of hydrogen atoms to obtain information on possible hydrogen bonding, and he felt that no conclusion could be drawn about hydrogen bonding based on the position of the other atoms.

Finally, he indicated that the conformation determined "represent(ed) the lowest energy state of the molecule in crystals of ephedrine hydrochloride, (while) the conformation proposed from chemical evidence (was) that which represent(ed) the lowest energy state of the molecule under the conditions of experiment."

Prompted by the work of Phillips, Kanzawa carried out extensive infrared studies on a series of substituted ephedrines and Ψ -ephedrines in the solid state and in carbon tetrachloride, chloroform, benzene, and carbon disulfide solutions.²⁸⁻³⁰ Systematic differences were evident between the substituted ephedrines and Ψ -ephedrines which allowed discrimination between the two series of related compounds and which gave some insight into the conformational arrangement in the molecules. Thus, in the solid state, the Ψ -ephedrine hydrochlorides showed $\nu_{\text{max}}(\text{OH})$ at about 100 cm⁻¹ lower frequency than the corresponding ephedrine hydrochlorides. This lowering of the OH stretching frequency was explained²⁸ as being due to hydrogen bonding in the crystal lattice.

Both series of compounds gave evidence of intramolecular hydrogen bonding in carbon tetrachloride and chloroform solution, although the Ψ -ephedrine compounds generally gave evidence of stronger bonding. Therefore, Kanzawa proposed that both isomers were in the gauche conformation and that ephedrine did not reside in the anti conformation with respect to the OH and NHCH₃ groups as previously supposed.

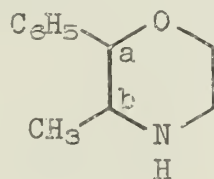
In 1958, Everett and Hyne reported the energetically preferred conformations for ephedrine and Ψ -ephedrine based on measurements of the dissociation constants of the ions of these two molecules in aqueous solution.³¹ This method was intended to give a measure of the repulsive interaction between non-bonded groups on C_O and C_N, ignoring specific interaction between the OH and NHCH₃ groups. As a result of their measurements, Everett and Hyne indicated their support for the anti disposition of the neutral ephedrine molecule but added that the ions of the two molecules would have the OH and NH₂CH₃ groups close together due to strong ion-dipole interaction.

Hyne later carried out an nmr study on ephedrine and Ψ -ephedrine. He initially reported²⁰ nmr temperature and concentration studies on the isomers by which he hoped

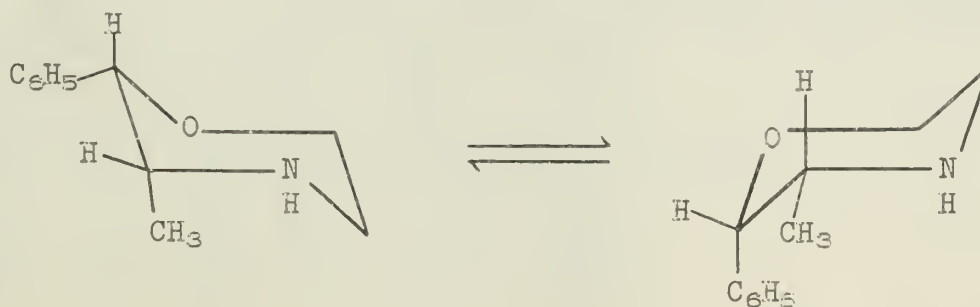
to show that any hydrogen bonding that did exist in the ephedrine case was largely intermolecular in nature. While the temperature studies were inconclusive, as they had been in Kanzawa's infrared studies, the concentration studies provided some interesting results. A plot of concentration versus frequency of NH/OH protons for ephedrine and Ψ -ephedrine indicated that the Ψ -ephedrine protons were at lower field than the ephedrine protons throughout the concentration range studied. It was also observed that at the lowest concentrations measured, Ψ -ephedrine approached a limiting frequency while ephedrine did not. This was taken to be good evidence for "preferential residence of the Ψ -ephedrine isomer in the gauche form compared with the ephedrine isomer" on the basis of the work of Huggins and coworkers.³² Their work on *o*-, *m*- and *p*-chlorophenols indicated that only in the *ortho* case did the frequency approach a limiting value, ostensibly due to hydrogen bonding.

In another nmr study,³³ Hyne cited the work on spin-spin coupling constants³⁴⁻³⁶ which indicated the existence of a correlation between the dihedral angle of two single protons on adjacent carbons and their coupling constant: 4.0 ± 0.2 and 8.2 ± 0.2 cps (in chloroform) for the ephedrine and Ψ -ephedrine isomers, respectively. He then used the theoretical calculations of Karplus³⁴ to obtain qualitative agreement with his previous hypothesis that the dihedral angle in Ψ -ephedrine was about 180° . The value that he obtained for (-)-ephedrine, however, indicated a dihedral angle of about 90° by the Karplus equation, which was a direct implication that the OH and NHCH₃ groups could not have an *anti* relationship. To accommodate this piece of evidence, Hyne postulated most favorable conformations for both which were somewhat different than the usual "pure staggered" conformations. These he called "off-staggered" conformations, by which he meant conformations somewhere between the normal staggered and eclipsed conformations. Thus Ψ -ephedrine was assigned a dihedral angle of 150 - 160° , which caused the OH and NHCH₃ groups to be 30 - 40° apart, and ephedrine was assigned a dihedral angle of 80 - 90° , which implied an angle of 80 - 90° between the OH and NHCH₃ groups. Although the latter assignment caused J_{calc} to be about 4 cps less than J_{obs} , Hyne felt that this difference could be explained in terms of two factors. The first of these was simply that calculated coupling constants always tended to be on the low side and the second was that ephedrine might well have a significant proportion of other conformational isomers present since little or no hydrogen bonding was apparent.

Recently Portoghesi³⁷ pointed out that, subsequent to the work of Hyne, Karplus had indicated the danger inherent in assigning a value to the dihedral angle simply on the basis of the vicinal coupling constant since other factors were found to affect J_{vic} .³⁸ Therefore, Portoghesi reinvestigated the nmr work of Hyne using "a closely related compound of known conformational preference," 3-methyl-2-phenyl-morpholine, as a standard of vicinal coupling. He also pointed out that at

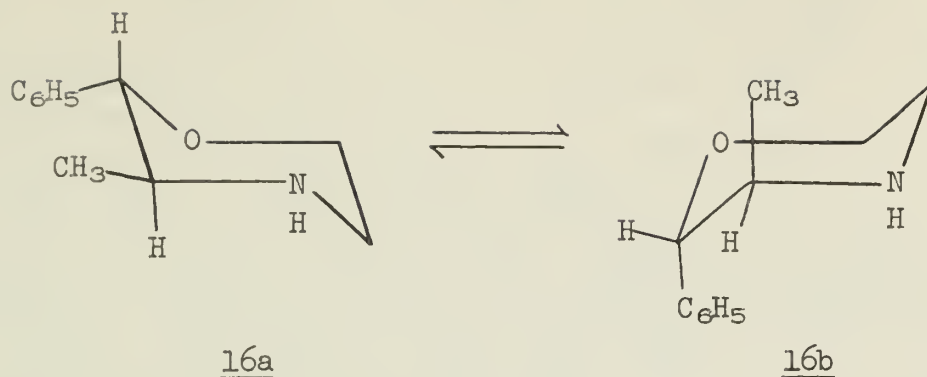


physiological pH a large portion of the molecules would be in ionized form, so that it would be a good idea to study the ephedrine salts as well.



15a

15b



It was demonstrated that small variations in J_{ab} which occurred in different solvents were probably due to factors other than conformation since $J_{ab(15)} - J_{ab(16)} = \Delta J_{ab} \approx \text{constant}$. It was also shown that, assuming a geometry of the morpholine ring similar to the chair form of cyclohexane, it was possible to obtain approximate values of ΔG for the equilibria $15a \rightleftharpoons 15b$ and $16a \rightleftharpoons 16b$ from known values of substituents in the literature. On this basis it was calculated that no less than 75% of each free base was in the equatorial phenyl conformation A, while each salt was calculated to exist in form A to the extent of 98%. These data, when applied to the coupling constants obtained from the morpholines and the ephedrine isomers, gave the result that the preferred conformation for both ephedrine and Ψ -ephedrine was the gauche conformation (of the OH and $NHCH_3$ groups) in both the protonated and unprotonated forms.

It was noted that both isomers appeared to be hydrogen bonded on the basis of the relative insensitivity of J_{ab} to solvent change. Nevertheless, the Ψ -ephedrine isomer should probably be thought of as having a greater proportion of its molecules in the preferred form than the ephedrine molecule, since in the former steric factors enhance intramolecular hydrogen bonding, while in the latter they oppose it.

CONCLUSION

A great deal of work has been carried out to determine the conformation of (-)-ephedrine and (+)- Ψ -ephedrine, most of which is incorrect. The conformation proposed on the basis of chemical evidence is incorrect because it assumes that the transition state energy for chemical reaction is always lower than the energy barrier to rotation, an assumption that is not justified for (-)-ephedrine in most cases. The actual conformation in both the protonated and unprotonated forms of these compounds seems to be that form which places the OH and $NHCH_3$ groups gauche to each other so that they may form a hydrogen bond while placing the remaining groups in whichever orientation yields the least non-bonded interaction.

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CATALYSIS OF ORGANIC REACTIONS BY DETERGENT MOLECULES

Reported by Stephen E. Rudolph

November 11, 1968

INTRODUCTION

In recent years a great deal of effort has been put into studies of systems in which aqueous solutions of detergents are observed to catalyze or inhibit organic reactions. A main source of the interest in this field is the fact that the behavior of these systems is in many ways similar to systems demonstrating enzyme catalysis. Principles learned from elucidation of the kinetics and mechanism of detergent catalysis may well be applicable to enzymatic systems. A further source of interest in detergent catalysis is the possibility that the use of detergent media may provide a useful means for directing the course of organic reactions. The purpose of this seminar, then, is to examine the properties of detergent molecules in solution with respect to the ability of such systems to influence the rates of organic reactions.

FORMATION OF MICELLES

It is well-known that detergent molecules in aqueous solution tend to aggregate into colloidal particles called micelles which contain approximately 30 molecules and have hydrocarbon interiors and charged surfaces.¹ Micelles of a given detergent form when the concentration of the detergent exceeds a certain value known as the critical micelle concentration (CMC). Since catalytic or inhibitory activity of a detergent is generally negligible at concentrations below the CMC, it can be said that the effects observed are due to interactions of micelles with substrate and that interactions between monomeric detergent and substrate are in general unimportant.²⁻⁴ For a typical ionic detergent dissociated in solution, with a long hydrocarbon chain and an ionic head group, the CMC is that concentration at which the energy released by the aggregation of the hydrocarbon chains of the monomers is large enough to balance the repulsion between ionic groups and the loss of entropy which accompanies aggregation.⁵ Obviously the presence of micelles in any system must represent the lowest free-energy state of that system.⁶ The CMC is evidenced by a more or less abrupt discontinuity in physical properties as the CMC is reached.⁷ For example, the CMC has been identified by the change in absorption of indicators near the CMC⁸ and by conductance studies which demonstrate that a plot of specific conductance vs. detergent concentration normally gives two nearly straight lines which intersect near the CMC.⁹ The behavior of detergent molecules below the CMC has been shown to be about the same as that of 1:1 electrolytes with no appreciable formation of dimers or ion pairs.⁷ In the presence of added substrates, however, micellization may sometimes occur slightly below the CMC and mixed micelles of substrate and detergent have been observed.¹⁰⁻¹¹

The size, shape, and properties of a micelle depend in part on the detergent molecules which form it, but all micelles have certain features in common. In general the micelle can be described as being composed of three distinct regions.¹²⁻¹³ The core or interior of the micelle is made up of the associating paraffin chains and resembles liquid hydrocarbon. The core is surrounded by an aqueous layer called the Stern layer which contains the ionic heads of the micellized detergent ions and a fraction of the counterions of opposite charge. For micelles of a typical detergent, sodium dodecyl sulfate (1), it has been shown that the thickness of the Stern layer corresponds within 1Å with the length of the hydrated ionic head of the micellized ions.¹³ Surrounding the Stern layer is a diffuse double layer called the Guoy-Chapman double layer which in effect neutralizes the charge of the Stern layer through the presence of an excess of counterions in the surrounding solution. Figure 1 shows a partial cross-section of a model of a micelle of 1 with hypothetical available sites for counterion binding.¹³

Evidence for considerable water in the Stern layer is provided by the results of a study of the hydrolysis of straight chain alkyl sulfates to the corresponding alcohols.¹⁴ The rate of this process was little affected by aggregation of the

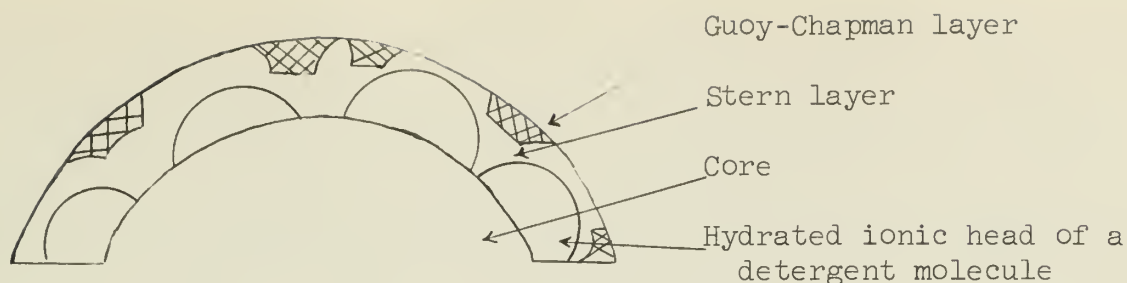


Figure 1. Model of a micelle of 1 with crosshatched areas representing available sites for counterion binding.

substrate molecules into micelles. This implies that at least as far in to the micelle as the α -carbon atom of the alkyl sulfate, where attack by a water molecule occurs, the water activity and solvating power of the medium are not appreciably different from those in the bulk aqueous phase. This supports the above model which pictures ionic head groups protruding from the hydrophobic core into a region where both counterion and solvent can penetrate. The presence of some water in the core of the micelle has been demonstrated by nmr studies.¹⁵

Factors controlling the size, shape, and ease of formation of micelles are not fully understood but it is thought that one important parameter is the size of the hydrated ionic head group. Micelles seem to form more easily as the size of the hydrated ion decreases.⁶ In addition, micellization is facilitated by compactness of the electrical double layer, i.e., by a lesser degree of ionization of the detergent molecule. These effects are apparently due to a reduction in electrostatic repulsive forces at the micelle surface.¹⁶ Small micelles are thought to be spherical but may grow into flexible rods as the core of the micelle changes from a spherical shape to an ellipsoidal shape with increasing degree of aggregation.¹²

EFFECT OF MICELLAR CHARGE ON EQUILIBRIA AND RATES

The catalysis of organic reactions by detergent micelles follows generally the pattern shown in Figure 2 for the sodium dodecyl sulfate catalysis of the acid hydrolysis of methyl orthobenzoate.³ As is evident from Figure 2, the rate constant is independent of detergent concentration below the CMC, increases rapidly after the

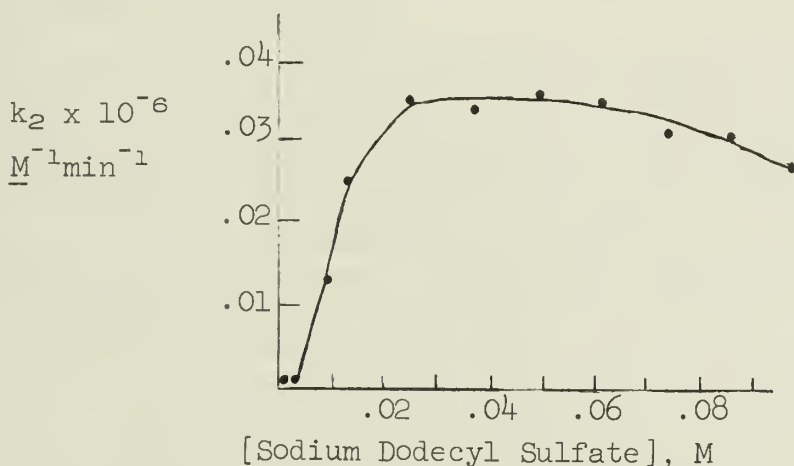
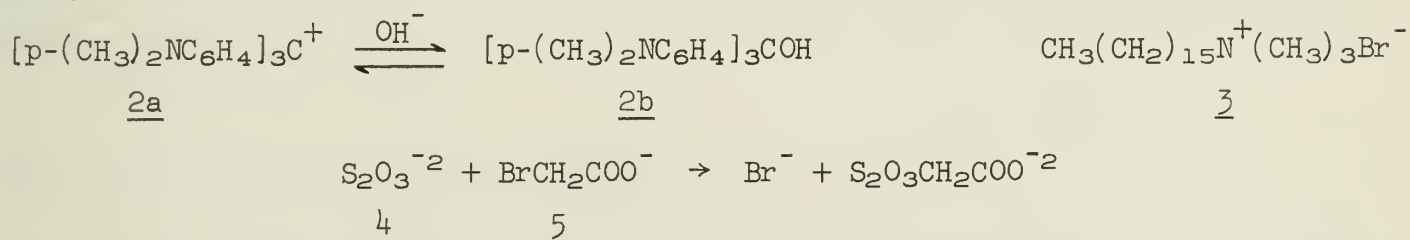


Figure 2. Second-order rate constants for hydrolysis of methyl orthobenzoate vs. concentration of sodium dodecyl sulfate. Values of pH were maintained at 5.40 with 0.01 M acetate buffers.

CMC is reached, levels off, and finally decreases at high detergent concentration. This behavior reveals that the important factors in such systems are (a) the necessity of the existence of micelles for catalysis to occur, (b) the adsorption of increasing amounts of substrate into the micellar phase until nearly all substrate is adsorbed and no further rate enhancement is seen, and (c) the inhibition of the catalytic effect at high detergent concentration. Reactions which are inhibited rather than catalyzed by micelles show a decrease in rate constants above the CMC which levels off at higher detergent concentration.

The general effect of an ionic micelle on a given process can be roughly

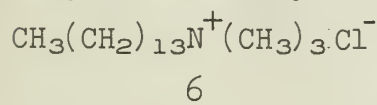
predicted on the basis of simple electrostatic effects. In 1934 Hartley developed a set of rules which determine the way in which the presence of a charged micelle will shift the equilibrium between the acidic and basic forms of indicators.¹⁷ Thus indicators having both colored forms positive or both negative are unlikely to be affected by positive and negative micelles, respectively. If the indicator is neutral in one form, it is expected to be displaced to the acid side by negative micelles and to the alkaline side by positive micelles. If both forms are of opposite sign to that of the micelle, the direction of the displacement is not readily predictable. These rules were derived by simply assuming preferential adsorption of one form of the indicator molecule onto the micelle with resulting displacement of the equilibrium in favor of that form. Duynstee and Grunwald found Hartley's rules to apply quite well to a study of the fading of triphenylmethane dyes in alkaline solution in the presence of micelle-forming salts.¹⁸ Thus the equilibrium between forms of crystal violet (2a,b) was shifted to the right in the presence of micelles of cetyltrimethylammonium bromide (3) and to the left in the presence of micelles of sodium dodecyl sulfate (1). Similarly, Hartley's rules correctly predict that anionic micelles should have little or no effect on the reaction between thiosulfate ion (4) and bromoacetate ion (5). The observed effect of anionic micelles on this reaction was about the same



as that observed for a solution containing an equivalent amount of simple electrolyte.¹⁹ These data indicate that the effect of micelles on equilibrium positions is largely electrostatic in origin. This is further supported by the fact that the hydrolysis of ethyl acetate, a reaction in which charged species do not interact, is not significantly influenced by the presence of micelles.²⁰ Application of these rules to the effect of micelles on rates of reactions requires that the charge type of the activation process be the same as the overall charge type of the equilibrium.

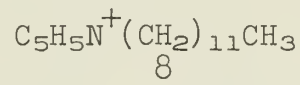
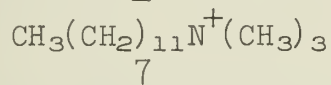
STRUCTURAL EFFECTS ON CATALYSIS

Since the catalytic process depends to a great extent upon the adsorption of the substrate onto the micelle, the structure of both substrate and detergent should be of importance. Substrate selectivity is indeed observed and a number of examples have been reported.^{3,8,21-23} A typical example is the observation that the acid hydrolysis of methyl orthobenzoate is catalyzed by detergent 1 while the hydrolysis of methyl orthoformate is not.²⁴⁻²⁵ This points out the importance of hydrophobic interactions in these systems. Since methyl orthoformate has no large hydrocarbon residues, hydrophobic interactions with the micelles are expected to be minimal and probably very little of this ortho ester becomes incorporated into the micellar phase, with the obvious result that little or no catalysis is possible. Methyl orthobenzoate, on the other hand, having a large hydrocarbon residue, can favorably interact with the detergent micelles and become incorporated into the micellar phase to a much larger extent and hence is subject to the catalytic effect of the micelles. Similarly, the basic hydrolysis of p-nitrophenyl hexanoate is much more subject to catalysis by tetradecyltrimethylammonium chloride (6) micelles than is that of p-nitrophenyl acetate.²³ In this case equilibrium constants for association of ester with micelles were estimated by measurement of the extent to which the detergent accelerated the passage of ester through a column



of Sephadex G-10. The equilibrium constants for association were approximated as $1.6 \times 10^4 \text{ M}^{-1}$ for p-nitrophenyl hexanoate and 33 M^{-1} for p-nitrophenyl acetate. The values correspond to about 3.7 kcal/mole difference in free energy for the transfer of the esters from the aqueous phase to the micellar phase. This value is reasonable on the basis of a reported favorable free energy change (1.4 kcal/mole) for transfer of a methylene group from aqueous to hydrocarbon medium.²⁶ In any case these data

support the reasonable assumption that the substrate selectivity is a result of greater tendency for association with micelles for one ester rather than any real difference in the reactivity of the two esters in the micellar phase. The structure of the detergent molecule from which the micelle is formed is also of importance. One major effect is that of detergent chain length.^{4,14,23,27} An increase in rate with increasing chain length was observed in the acid hydrolysis of alkyl sulfates.¹⁴ In this case the substrate was also the micelle-forming agent, and the rate increase was attributed to an increase in size and tightness of the micelle resulting in an increase in the micellar potential. In cases where the detergent molecule and substrate molecule are not one and the same, the increase in catalysis with increasing chain length may also be due to the importance of the hydrophobic interactions between substrate and detergent or to factors such as the positioning of substrate with respect to the micelle.²³ The nature of the head group of the detergent also seems to exert an effect. The hydrolysis of p-nitrophenyl hexanoate is catalyzed to a much greater extent by n-dodecyltrimethylammonium ion (7) than by n-dodecylpyridinium ion (8).⁸ One possibility for the difference in catalytic ability between 7 and 8 is that because of the bulk and flatness of the detergent heads in 8 the micelles may be unusually loose structures and may contain considerably more water than micelles of 7.



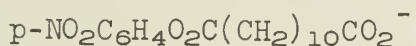
ASSOCIATION BETWEEN SUBSTRATE AND MICELLE

Attempts at explaining the catalysis and inhibition demonstrated by systems containing micellized detergents are frequently complicated by an uncertainty in the exact nature of the association between substrate and micelle. Mukerjee and Mysels observed the formation of a simple salt between pinacyanol dye ions and 1 below the CMC.¹⁰ Above the CMC no salt was evident, apparently due to solubilization of the salt by mixed micelles of dye and detergent. Spectral evidence for interaction between substrate and micelle was presented by Duynstee and Grunwald.¹⁸ When the charge on the triphenylmethane dye being studied was opposite to that of the detergent micelle a significant red shift was observed in the absorption spectrum of the dye. Such a red shift is consistent with a change from aqueous to hydrocarbon media²⁸ and was attributed to actual incorporation of the dye ion into or onto the oppositely charged micelle. Data are available, however, which show that it may be very difficult to distinguish between adsorption of the dye into the interior of the micelle and onto the surface of the micelle in the above case. Mukerjee and Ray studied the position of charge transfer bands for the iodide salt of 8 and found a significant red shift for this species in comparison to the band position for methylpyridinium iodide.²⁹ Since this was shown not to be a chain length effect, the most acceptable explanation is that there is a considerable reduction in polarity at the micelle surface, where the charge transfer interactions occur, with respect to the polarity in the bulk aqueous phase. The effective dielectric constant at the surface of the micelle was estimated at 36 ± 2 by comparing the band positions of non-micellized 8 in solvent mixtures of different dielectric constants to that of the micelles in aqueous solution. While it is hard to extend these data in any quantitative way to micelles of other detergents, it seems likely that a general property of the Stern layer must be a considerably lower polarity than that of the bulk aqueous phase.

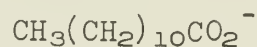
Erikson and Gillberg have reported nmr data which seem to indicate that whether a substrate is adsorbed into the micelle interior or onto the Stern layer of the micelle depends on the precise nature of the substrate.³⁰ In this study resonance line widths and positions for micelles of 3 were examined in the presence of solubilized substrates of different structure. Large shifts of line positions of the α -hydrogens of the detergent molecules in these micelles were attributed to adsorption at the micelle surface and were observed for several aromatics including benzene and nitrobenzene. On the other hand, saturated hydrocarbons gave much smaller line shifts and were assumed to be adsorbed into the micellar interior. It was concluded that the large shifts to higher fields caused by aromatic substrates were a result of these molecules

replacing water molecules in the Stern layer near the α -hydrogens of the detergent molecules. The saturated species, lacking the polarizability of the aromatic ring, are thought to be unable to accomplish the replacement of water near the hydrocarbon core of the micelle and hence are adsorbed into the interior of the micelle. Other data³¹ also point to the possibility that just above the CMC, where a very loose micelle structure probably exists, adsorption at the surface of the micelle may occur for substrates which would be expected to be adsorbed much deeper into the micelle at higher detergent concentration.

Kinetic data interpreted in terms of the adsorption of substrate into the micelle core have been presented. Menger and Portnoy studied the basic hydrolysis of mono-p-nitrophenyl dodecanedioate (9) in the presence of micelles from laurate anion (10).⁸ Figure 3 shows the inhibition caused by increasing concentration of (10) on the basic hydrolysis of (9). The overall process is represented by a scheme which recognizes



9



10

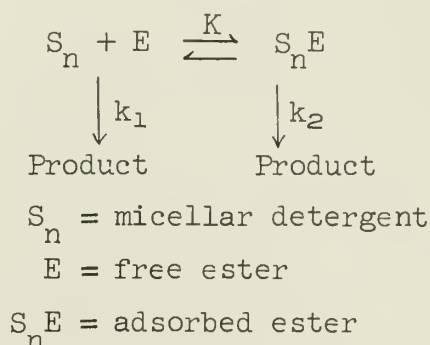
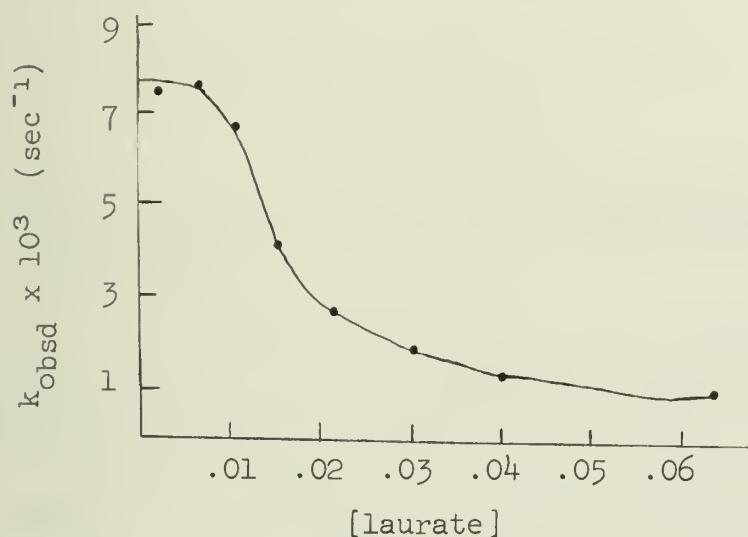


Figure 3. Plot of observed rate constant for the hydrolysis of (9) at pH 9.59 vs. concentration of laurate.

the distribution of ester between aqueous and micellar phases. The concentration of micelles can be calculated if it is assumed that the average number of laurate ions per micelle is 33. The observed rate constant can then be related to the rate

$$\text{S}_n = \frac{[\text{laurate}]_t - \text{CMC}}{33}$$

$$\frac{1}{(k_1 - k_{\text{obsd}})} = \frac{1}{(k_1 - k_2)} + \frac{1}{(k_1 - k_2)KS_n}$$

$[\text{laurate}]_t$ = total concentration of laurate

constants for reaction in the presence and absence of detergent. The rate constant for adsorbed substrate, k_2 , is evaluated by plotting $1/(k_1 - k_{\text{obsd}})$ vs. $1/\text{S}_n$ using the measured values of k_1 (rate constant in the absence of detergent) and k_{obsd} (rate constant in the presence of detergent). This plot is given in Figure 4. Figure 4 is remarkably linear when it is considered that five assumptions were made in this treatment of the data. These assumptions were (a) the substrate does not complex with detergent monomer, (b) the substrate does not in any way perturb the micellization process, (c) substrate associates with the micelles in 1:1 stoichiometry, (d) micellization occurs exactly at the CMC and not over a small interval around the CMC, and (e) the concentration of unassociated detergent remains constant above the CMC. The intercept of the plot in Figure 4 is within experimental error of $1/k_1$, indicating that the rate constant for the hydrolysis of the ester must be zero when the ester is adsorbed into the micelles. This is interpreted as indicating that the ester substrate is adsorbed into the hydrocarbon interior of the micelle, i.e., positioned in the micelle in much the same way as the laurate molecules are.

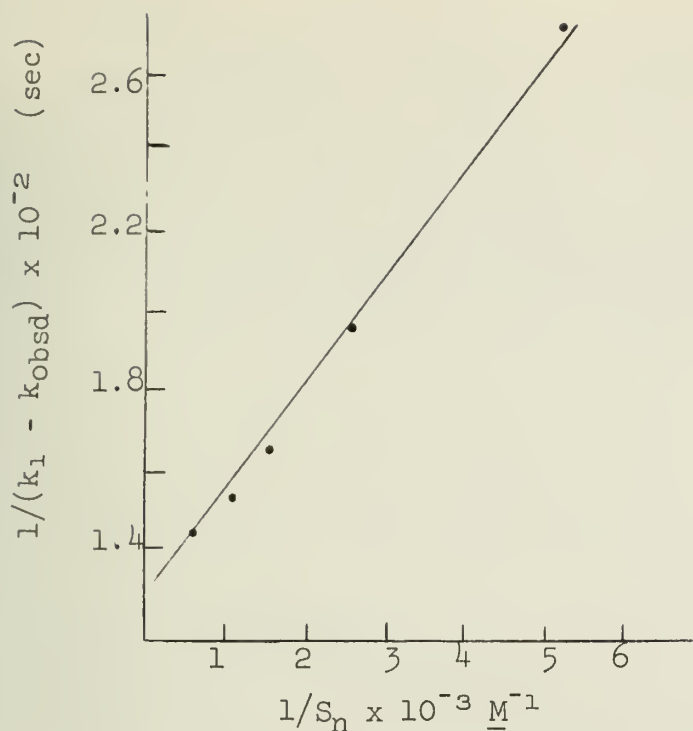


Figure 4. Determination of the rate constant for hydrolysis of adsorbed mono-p-nitrophenyl dodecanedioate.

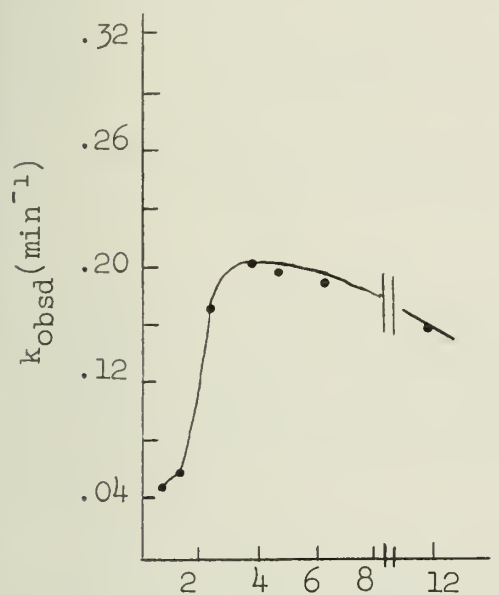
Such positioning would place the ester function well into the hydrocarbon core where there is expected to be no anionic nucleophile. While hydroxide ion concentration should also be greatly reduced at the outer aqueous portions of the micelle due to electrostatic repulsion, adsorption taking place in this region is regarded as being less likely since a high concentration of carboxylate anion, which can catalyze ester hydrolysis intramolecularly, is present. In view of this the rate constant of zero in the micellar phase supports adsorption of the ester into the micelle interior. A similar interpretation can be made of the data of Winters and Grunwald which estimated the rate of reaction of methyl bromide with CN^- as zero in the presence of micelles of L^- .³²

Other workers, however, maintain that adsorption must occur at the Stern layer of the micelle and not within the interior of the micelle,³ partially because observed salt effects on the rates of micellar reactions are difficult to explain on the basis of substrate adsorbed into the micellar interior. These salt effects are discussed in detail below.

Whether the main site of substrate adsorption is the Stern layer or the micelle interior, most catalyses of organic reactions can be explained at least qualitatively in terms of electrostatic interactions between substrate and micelle. Alterations in the stability of reactants and of transition states incorporated into micelles may be of very great importance.³³ Kurz attributed rate enhancement of the acid-catalyzed hydrolysis of micellized long chain alkyl sulfates to an increased basicity of the sulfate moieties due to the presence of the negative potential of the micelle.¹⁴ Cordes explains the effects of micelles on hydrolyses of methyl orthobenzoate³ and p-nitrophenyl hexanoate²³ in terms of stabilization of the reaction transition state by the oppositely charged micelle surface. This effect may in fact be a major effect operating in a number of such systems.³³⁻³⁴ This concept is supported by some thermodynamic data showing that lowering of the enthalpy of activation in such processes is the major thermodynamic effect taking place.^{3,14,20-21} Other data, however, suggest only a very small change in the enthalpy of activation but quite a large change in entropy of activation.³⁵ In any case thermodynamic data in such complicated systems are often very hard to interpret, and the thermodynamic quantities obtained are undoubtedly dependent upon a number of factors which are not yet fully understood. In addition to electrostatic effects, including the effect of the micelle surface acting as an area of high concentration of charge for attracting or repelling reactant ions, medium effects may also be important. For example, for different detergents the micelle shape and structure will exert different influences on the medium in and around the micelle as will different concentrations of the same detergent.³⁶ Although it is generally assumed that one molecule of substrate is incorporated per micelle, differences in this factor between different detergents and substrates may account in part for the variation in catalytic activity of different systems. Closeness of the reactive site to the hydrophilic part of the micelle may also in part influence the effect of micelle on substrate both for detergent adsorption onto the surface of the micelle and into the interior.³⁷

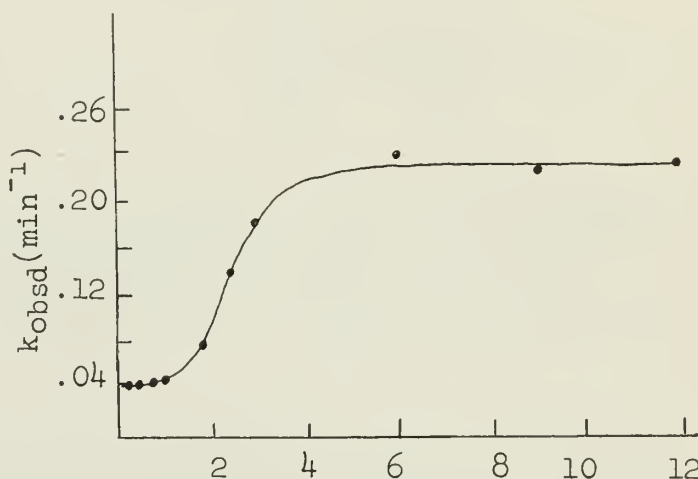
SALT EFFECTS

The inhibition of catalysis at high detergent concentration has received considerable attention. Figure 5 shows that increases in detergent concentration above a certain level result in a decrease in the value of the measured rate constant for the basic hydrolysis of p-nitrophenyl hexanoate.²³ Figure 6 shows that the decrease in rate constant is due to increasing concentration of detergent counterion since the effect disappears when counterion concentration is held constant. Inhibition of this process is also caused by other anions and the order of inhibitory capacity is $\text{NO}_3^- > \text{Br}^- > \text{Cl}^- > \text{F}^-$. At high concentration NO_3^- and Br^- actually



[tetradecyltrimethylammonium bromide] x 10³ (M)

Figure 5. First-order rate constant for the basic hydrolysis of p-nitrophenyl hexanoate at pH 10.07 vs. concentration of tetradecyltrimethylammonium bromide.



[tetradecyltrimethylammonium chloride] x 10³ (M)

Figure 6. First-order rate constant for the basic hydrolysis of p-nitrophenyl hexanoate at pH 10.15 vs. concentration of tetradecyltrimethylammonium chloride at a constant total chloride ion concentration of 0.02 M.

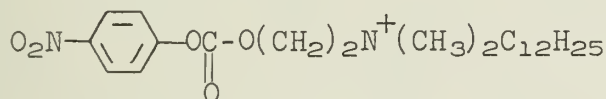
reduce the rate level below that observed in the absence of detergent. Similar effects for high concentrations of cations on the rate constant for acidic hydrolysis of methyl orthobenzoate in the presence of 1 have been reported.³ Results for a large number of cations showed that (a) for alkali metal cations inhibitory effectiveness decreases with increasing size of the hydrated ion, (b) for alkaline earth cations, inhibitory effectiveness is largely independent of the nature of the cation, and (c) for ammonium ions of all types inhibitory properties increase with increasing hydrophobic character of the ion. These effects were attributed to a decrease in the electric field at the surface of the micelle caused by a high concentration of counterions. This is supported by studies which show that, at least for the addition of alkali cations to anionic detergents, the CMC is decreased,³⁸ and the micellar size is increased.³⁹ Both these effects are expected consequences of a reduction in surface electric field. Such a reduction in surface potential is expected to influence the reaction rate by decreasing the ability of the micelle to stabilize the oppositely charged transition state for the reaction, assuming that such stabilization is the major effect exerted by the micelles on the reaction. For any process involving small charged ions, such as these acid and basic hydrolyses, the lowering of the micellar concentration of such ions due to lowered electric potential at the micelle surface and the increased competition with salt ions for available sites must also play an important role in the observed salt effects.

Salt effects have been attributed to other factors, the most common being a lowering of the rate level due to exclusion of the substrate from the micellar

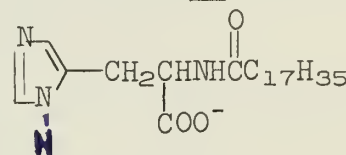
phase.⁴⁰⁻⁴¹ An argument against this is that equilibrium constants for distribution of substrate between aqueous and micellar phases are generally little affected by salt concentration and that salt effects sometimes lower the rate level below that in the absence of detergent.^{3,23}

SIMILARITIES TO ENZYMATIC SYSTEMS

The similarities of micellar systems to enzymatic systems are remarkable. Besides the fact that enzymes and micelles are of approximately the same molecular weights, both show substrate selectivity, saturation of catalyst with substrate and saturation of substrate with catalyst,²⁴ and both show inhibition by ions. Several studies have been made in which attempts were made to approximate specific enzyme behavior within a micellar system.^{22,42-45} One such study⁴² demonstrated that the release of p-nitrophenol from substrate (11) by N-stearoylhistidine (12) is about



11



12

240 times as effective as the release by N-acetylhistidine. The rate enhancement is apparently due to apolar interactions between lyophobic groups in the substrate-catalyst complex. This system demonstrates saturation phenomena, selectivity, inhibition by NaCl, and further resembles enzyme catalysis in that denaturation of the catalysis by urea is observed.

APPLICATIONS

Detergent catalysis is potentially a powerful tool for use in the control of organic reactions. There are several advantages to the use of an aqueous solution of a detergent of suitable charge type as the reaction medium of choice: (a) lower cost than an organic solvent of suitable solvating power, (b) fewer side reactions in the aqueous medium than in organic media, and (c) changing the nature or concentration of detergent gives additional variables which can be used to control the rate of reaction and the final equilibrium position.⁴⁶ It has been demonstrated that a reaction may be cycled through repeated accelerations and inhibitions by adding detergents of opposite effects in successively increasing concentrations.⁴⁷

CONCLUSION

Detergent catalysis is a process which depends upon the formation of micelles and the development of favorable interactions between hydrophobic and hydrophilic portions of substrate and micelle. Since a distribution of substrate between aqueous and micellar phases results, observed rate constants consist of terms from the reaction of both free substrate and micellized substrate and are difficult to evaluate quantitatively. The major effect of a micelle in many cases seems to be a lowering of the activation energy for the process being catalyzed.

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THE SYNTHESIS OF ECDYSONE

Reported by Robert Farney

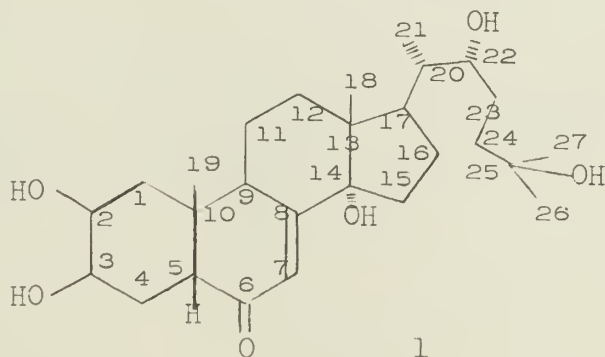
November 18, 1968

The study of the chemical constituents of insects has recently become an active area of interest, centered primarily on two classes of substances: insect pheromones and insect hormones. Insect pheromones are chemical substances which act as messengers between individual insects of the same species,¹ sex attractants and defense secretions being two examples. Insect hormones differ from pheromones in that hormones are chemical substances that relate various organs and processes within an individual insect. The insect juvenile and moulting substances are examples of insect hormones.

The regulation of the growth and form of insects by hormones, particularly by the moulting and juvenile hormones, is a fascinating subject and the reader is urged to consult the excellent reviews available.¹⁻³ Briefly stated, an insect develops from a larva stage to a pupa and finally to an adult form. This metamorphosis is regulated by the presence or absence of the moulting and juvenile hormones and is characterized in part by a change in the nature of the insect cuticle. The simultaneous presence of both hormones causes an insect larva undergoing metamorphosis to develop a pupa type of cuticle; the presence of the moulting hormone alone, by contrast, results in the development of an adult cuticle. Moulting hormones function as DNA activators in that their presence in the cell nucleus indirectly results in the synthesis of two specific enzymes. In turn, these enzymes bring about hardening or sclerotization of the insect cuticle with its subsequent loss.³

Early investigations into the chemical nature of the moulting hormones were hampered by the extremely minute quantities of material that could be extracted from insects. From 500 kg of silkworm papae, for example, Butenandt and Karlson were able to isolate only 25 mg of crystalline material.⁴ Since that time, however, moulting substances have been isolated from a variety of sources.⁵ In fact, the plant kingdom has virtually replaced insects as the major source of substances showing insect moulting activity. Of the seventeen known moulting materials, all seventeen are found in quantity in plants, while only three have been found in insects. Although the suspicion that insect moulting hormones occur as glycosides in plants was recently confirmed,⁶ there is still no adequate explanation for their presence in plants.⁷

The first moulting hormone to be isolated whose structure was determined was ecdysone,^{4,8} 2 β , 3 β , 14 α , 22R, 25-pentahydroxy- Δ^7 -5 β -cholesten-6-one, C₂₇H₄₄O₆, 1. The structural features of ecdysone--a sterol containing a 2 β , 3 β -glycol, an A/B-cis ring junction, a 7-ene-6-one function, a 14 α -hydroxyl group, and a hydroxylated side chain--are characteristic of the insect moulting substances. Generally the



insect moulting substances differ only in (a) the number, position, and configuration of side chain hydroxyls, and (b) the extent of side chain alkylation, some moulting substances containing an additional methyl or ethyl group not found in ecdysone. Only three substances known to display insect moulting activity are exceptions to these

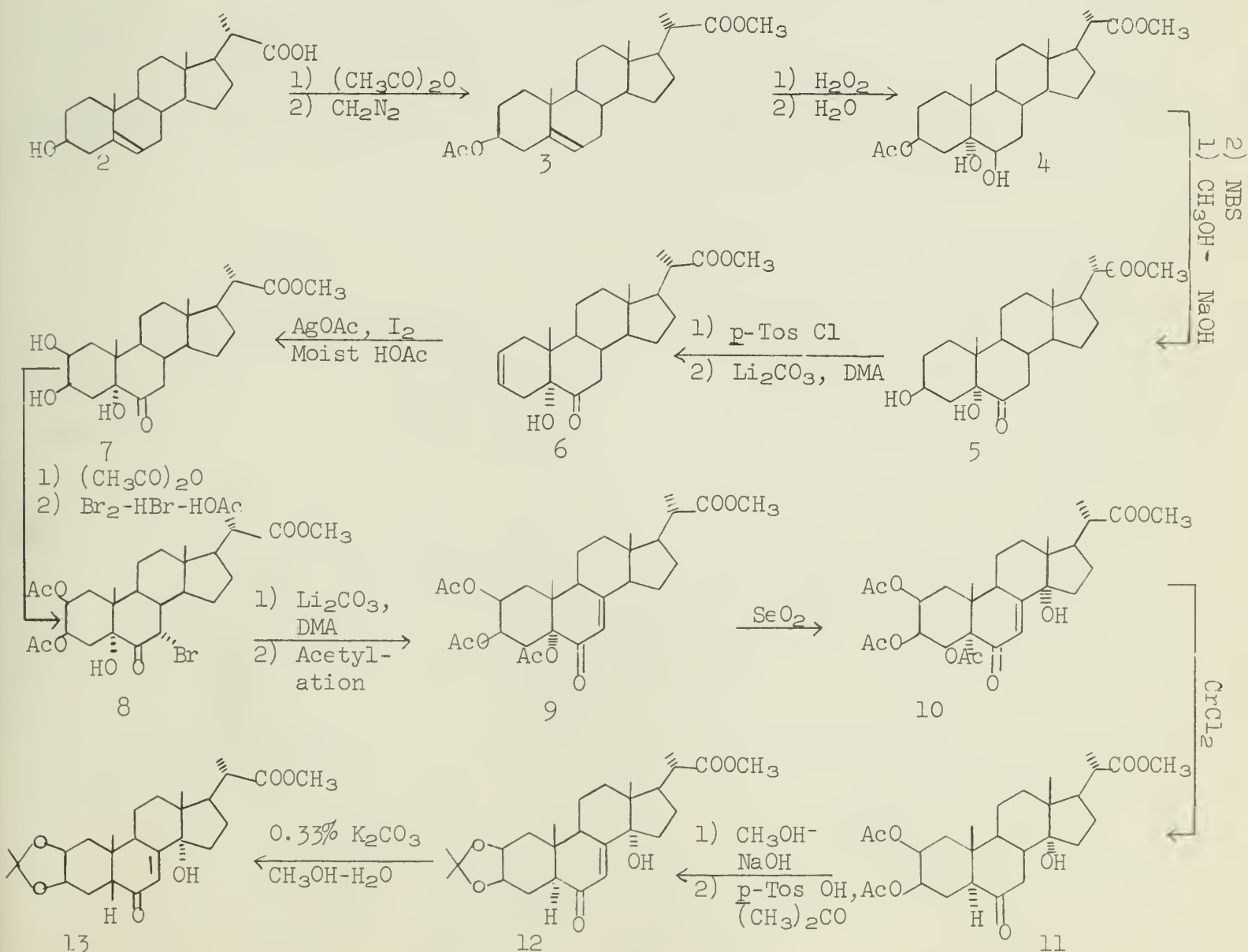
characteristics.⁹⁻¹¹

Unfortunately few analogs of ecdysone have been assayed for biological activity, and thus structure-activity correlations may be premature. However, it appears¹ that of the five hydroxyl groups contained in ecdysone, only the vicinal glycol function is essential for biological activity. Although ecdysone-like compounds of the 5 α series are biologically inactive, 17-ketoeecdysone (rubrosterone) is active. Steroids which inhibit postecdysial hardening and sclerotization and thus appear to be molting hormone antagonists have recently been synthesized.¹²

The interesting biological activity of ecdysone, the unusual structural features of the ecdysone molecule including its ten asymmetric centers, and the need for an ecdysone-like skeleton which could be altered to establish structure-activity correlations in the insect molting hormones provided stimuli for the synthesis of this compound. There are three known synthetic routes to ecdysone.¹³⁻¹⁵ Each synthesis recognized three problem areas: (a) the synthesis of the 2 β , 3 β -diol, A/B-cis moiety, (b) the introduction of the 7-ene-6-one and 14 α -hydroxyl functional groups, and (c) the synthesis of the hydroxylated side chain.

Ecdysone was first synthesized by Siddall *et al.*¹³ According to this plan, all functional groups were introduced into the perhydro-5 α -cyclopentenophenanthrene skeleton before the A/B juncture was equilibrated from the trans to the cis configuration (Sequence I). Because of the steric repulsion between the 2 β -acetonide and the C-19 methyl in the trans acetonide 12, this equilibration favored the thermodynamically more stable cis configuration 13. The side chain was then introduced as shown in Sequence II.

Sequence I

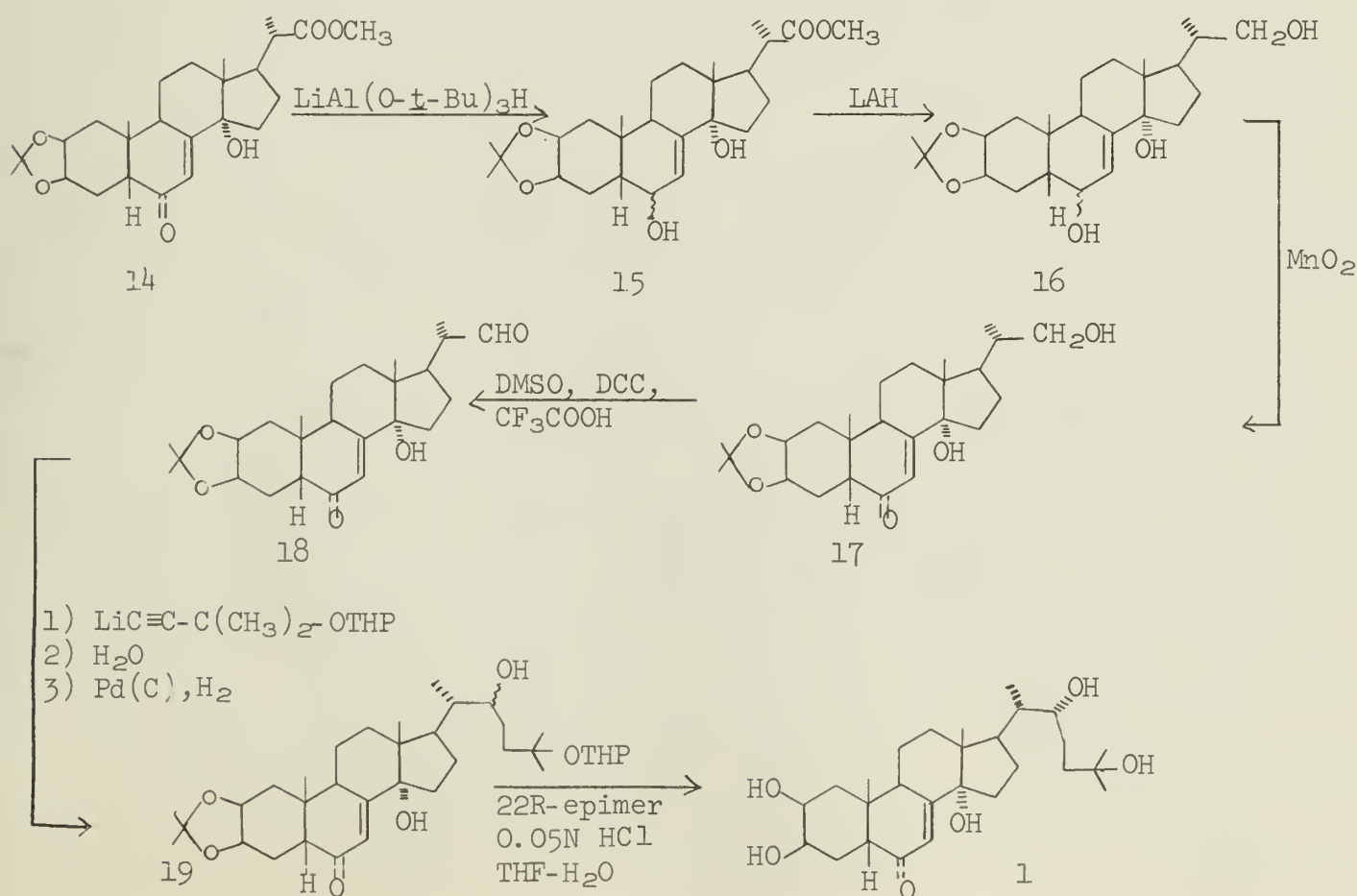


3 β -acetoxy-23,24-bisnorchol-5-en-22-oic acid methyl ester 3 was prepared in quantity from 3 β -hydroxy-23,24-bisnorchol-5-en-22-oic acid 2 by successive acetylation and methylation. Transformation to the trans-diol 4 according to the method of Fieser,¹⁶ followed by mild alkaline hydrolysis, yielded the 3 β (e=equatorial), 5 α (a=axial), 6 β (a)-triol. In sterols, axial alcohols are more easily oxidized by N-haloimides than their equatorial epimers due to the greater accessibility of the C-H bond in the former.¹⁷ Thus, oxidation of the triol corresponding to 4 by treatment with N-bromosuccinimide in aqueous dioxane gave 5, completing the introduction of the 6-one functionality in the B ring.

Introduction of the 2 β (a), 3 β (e)-cis glycol function was achieved by treatment of the 6-keto-5 α -hydroxy-23,24-bisnorchol-2-en-22-oic acid methyl ester 6 according to the method of Prévost.¹⁸ Acetylation followed by hydrogen bromide catalyzed bromination gave the 7 α -bromo-6-one 8. Dehydrobromination (lithium carbonate in dimethylacetamide) and acetylation gave the 7-ene-6-one 9. The 14 α -hydroxyl group was introduced by allylic oxidation with selenium dioxide in dioxane.¹⁹

Treatment of the 5 α -acetate 10 with chromous chloride resulted in stereospecific α -face replacement of the acetate by hydrogen to give 11. Chromous chloride has found wide applicability in steroid synthesis as a mild reducing agent, replacing the use of zinc-acetic acid which cannot be used to reduce acid-sensitive compounds. Chromous chloride has been used successfully to eliminate vicinal dihalides, to reduce α,β -epoxyketones to the α,β -unsaturated carbonyl compounds, and to reduce α -bromoketones to the corresponding unsubstituted carbonyls.²⁰ Following conversion to the 2 $\beta,3\beta$ -acetonide 12, equilibration of the A/B-trans junction with 0.33% potassium carbonate in aqueous methanol gave a 3:1 mixture of the desired 5 β compound and recovered starting material. At this point the tetracyclic skeleton of ecdysone was complete. Attachment of the side chain to obtain the biologically active material proceeded as outlined in Sequence II.

The C-22 position in the sterol molecule is a hindered position.²¹ For example, in the case of the bisnor acids this hindrance is revealed by extremely slow ester hydrolysis. Thus reduction of 14 with the highly selective tri-*t*-butoxy lithium aluminum hydride resulted in reduction of the relatively unhindered 6-keto group. Further

Sequence II^{13c}

reduction with lithium aluminum hydride reduced the 22-carbomethoxyl group, after which the 6-one could be regenerated by oxidation of 16 with manganese dioxide, an extremely mild oxidizing agent specific for allylic alcohols.²² When 17 was treated with dimethyl sulfoxide and dicyclohexylcarbodiimide with acid catalyst, oxidation of the 22-ol to the aldehyde occurred. The use of DMSO as an oxidizing agent is particularly applicable to acid- and base-sensitive sterols and also in the oxidation of α -haloketones, α -haloesters, alkyl halides and tosylates, benzylic alcohols, and epoxides.^{23, 24}

Treatment of the C-22 aldehyde 18 with the lithium salt of 3-methyl-3-(tetrahydropyran-2-yloxy)-1-butyne followed by catalytic hydrogenation gave 19 as C-22 epimers; the isomers were separated by silica gel thin layer chromatography. Mild acidic hydrolysis of the 22R epimer of 19 released ecdysone 1.

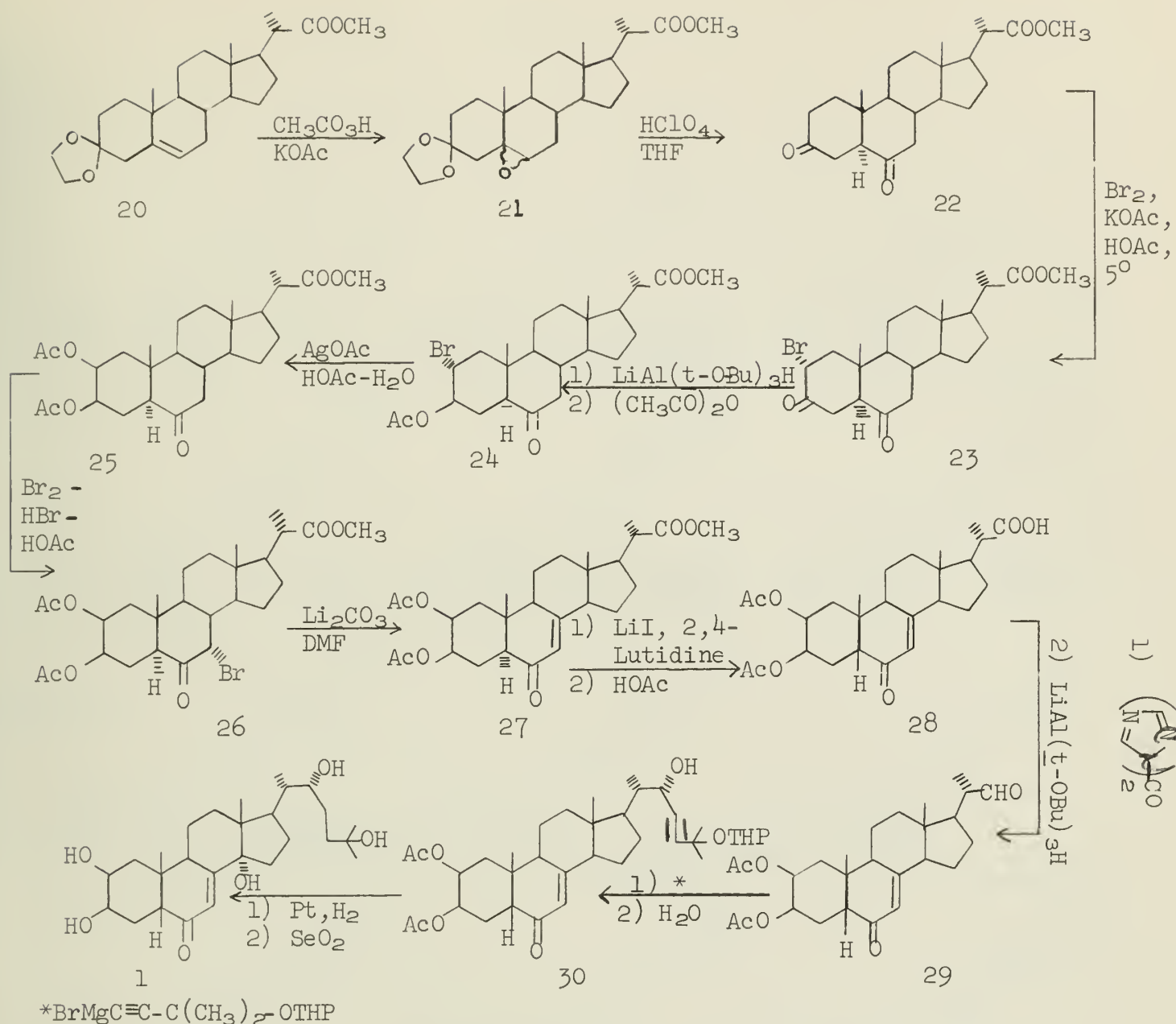
An earlier method of attaching the side chain^{13b} utilizing the salt of an α -methylene sulfoxide as the alkylating agent resulted in epimerization of the C-20 center. Earlier work²¹ has shown that C-22 methyl ketones isomerize readily via the enol in the presence of base. Attachment of the alkyl chain via the less basic 1-butyryl salt apparently avoids epimerization at the C-20 center, since ecdysone and its C-22 epimer were the sole products obtained following hydrogenation and hydrolysis.

The synthesis of ecdysone as described by Weichert et al.¹⁴ is outlined in Sequence III. Preliminary experiments showed that both 2 β ,3 β -dihydroxy-5 α -cholestan-6-one and the corresponding 2-acetoxy compound could be equilibrated to a 1:1 mixture of the 5 β (A/B-cis) isomer and starting material by 3N HCl-CH₃OH treatment. This equilibrium reflects the steric repulsion between the 2 β (a) hydroxyl group and the C-19(a) methyl group. Furthermore, it was found that corresponding compounds of the 5 β (A/B-cis)- and 5 α (A/B-trans)-6-one could easily be distinguished by optical rotary dispersion curves and mass spectra. In contrast to the reports of Siddall et al.¹³ however, in many cases the Weichert group was unable to distinguish corresponding A/B-cis from A/B-trans compounds by the nmr chemical shifts of the C-18 and C-19 angular methyl groups.

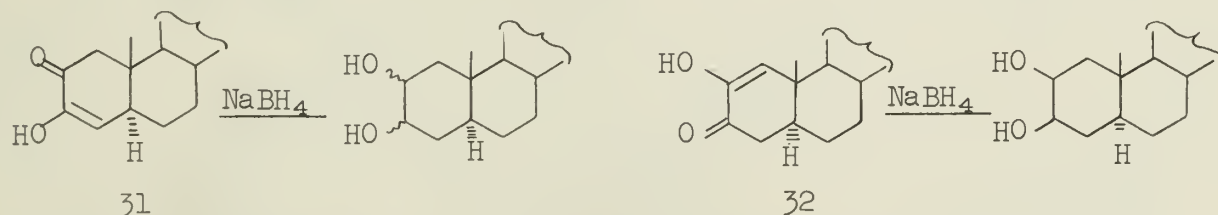
(20S)-3,3-Ethylenedioxy pregn-5-ene-20-carboxylic acid methyl ester was converted to the 3,6-dione 22 via the epoxide mixture 21. Careful low temperature treatment of the dione with bromine in acetic acid in the presence of acetate ion gave the sterically favored 2 α (e)-bromo product 23. The less hindered 3-keto function could be reduced selectively with tri-t-butoxy lithium aluminum hydride. Treatment of the 2 α (e)-bromo acetate 24 under modified Prevost reaction conditions¹⁸ gave the 2 β ,3 β -diacetate as shown by the chemical shifts of the protons geminal to the acetate groups. Partial inversion of the C-5 center also occurred at this point to give a 1:1 mixture of the 5 α and 5 β isomers which were separable by fractional crystallization. After introduction of the 7-ene function by bromination and dehydrobromination, the hindered C-22 carbomethoxyl group of 27 was de-esterified by lithium iodide halogenolysis, a reaction involving the nucleophilic displacement of the steroid carboxylate ion from the ester methyl group. Such lithium iodide halogenolyses are ideal for sterically hindered, acid- or base-sensitive esters.²⁵ However, in this case partial epimerization of the C-5 and C-20 centers also occurred, although the isomers were readily identified via ORD and nmr and were easily separated by chromatography on silica gel. The carboxyl group of 28 was reduced to the aldehyde stage by treatment first with N,N'-carbonyldiimidazole to form the C-22 acylimidazole, followed by reduction with one equivalent of tri-t-butoxy lithium aluminum hydride. No reduction to the corresponding alcohol occurred.²⁶ (Note that this same reduction required four steps in the procedure of Siddall et al. (14-18). Treatment of 29 with (3-methyl-3-(tetrahydropyran-2-yloxy)-1-butyryl)magnesium bromide gave 30 in a ratio of C-22(R):C-22(S) of 2:1; predominance of the (R) isomer is expected according to the principles of asymmetric induction. Following separation of isomers and hydrogenation of the triple bond, oxidation by selenium dioxide in dioxane removed all protecting groups and introduced the 14 α -hydroxyl group to give ecdysone 1.

The synthesis of ecdysone described by Mori et al.¹⁵ involves an unusual method of introducing both the 2 β ,3 β -diol function and the dihydroxylated side chain of ecdysone. Preliminary experiments showed that sodium borohydride reduction of the 3-ene-3-ol of 5 α -cholestan-2-one 31 gave the four epimeric 2,3-diols in approximately equimolar mixture. However, sodium borohydride reduction of the tautomer 1-ene-

Sequence III



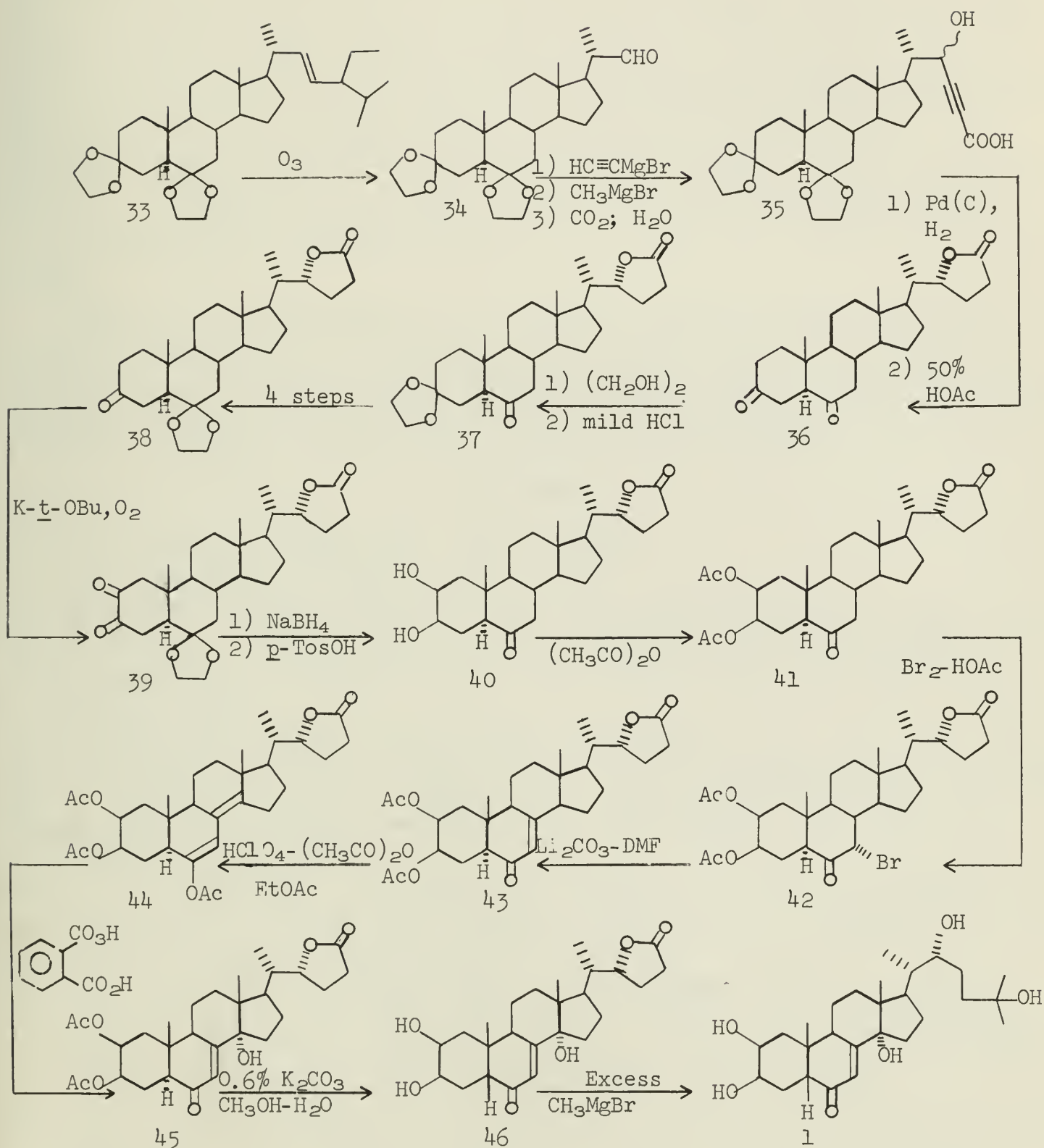
2-ol of 5 α -cholestan-3-one 32 gave predominately (90%) the synthetically useful 2 β ,3 β -diol. The problem of introducing the 2 β ,3 β -glycol function into the developing ecdysone skeleton therefore became one of obtaining the corresponding 2,3-dione.



Known methods of introducing a carbonyl alpha to a ketone usually proceed in poor yield and hence were passed over in favor of a potassium *t*-butoxide catalyzed autooxidation of a 3-one. The complete synthesis of ecdysone according to Mori *et al.*, is given in Sequence IV and is further distinguished by the introduction early in the synthesis of the hydroxylated side chain in the form of a δ -lactone.

The diketal of stigmast-22-ene-3,6-dione 33 was ozonized to the C-22 aldehyde. Two successive Grignard reactions gave the epimeric (at C-22) α,β -acetylenic acids. Hydrogenation and lactonization followed by diketalization and mild acid hydrolysis gave the (22R)-3-monoketal 37, which could be separated from its C-22 epimer by fractional crystallization. The (22R)-3-monoketal was transformed to the 6-monoketal in four steps involving a sodium borohydride reduction and an oxidation by the chromium

Sequence IV



trioxide-pyridine complex. Autoxidation of 38 to the enol mixture of diosphenols occurred when a t-butyl alcohol solution of 38 was shaken in an oxygen atmosphere in the presence of potassium t-butoxide. Without separation of the enol forms, the diosphenol was reduced via sodium borohydride to a mixture of the 2,3-diols, from which the desired 2 β ,3 β -diol was obtained by preparative thin layer chromatography. Following acetylation, the 7-ene was introduced by the usual bromination and dehydrobromination.^{13a,14b} Perchloric acid catalyzed acetylation to the conjugated enol acetate 44 occurred when 43 was treated with an acetic anhydride-ethyl acetate solution 10^{-3} M in perchloric acid. This is a highly effective method of acetylating even hindered alcohols, thiols, phenols, and amines; the reactive species is believed to be the acetylum $(\text{CH}_3\text{CO})^+$ ion.²⁷ The enol acetate then isomerized smoothly to the 14 α -hydroxy- Δ^7 -ene-6-one when treated with a slight excess of monoperphthallic acid. Equilibration of the A/B-trans ring junction was effected by refluxing in 0.6% potassium carbonate in aqueous methanol, yielding a more favorable ratio of the A/B-cis to A/B-trans compounds (4:1) than reported by Siddall (3:2)^{13a} or Weichert (1:1).^{14a} Isolation of the 5 β isomer by preparative thin layer chromatography followed by treatment with excess methylmagnesium bromide gave ecdyson, identical in all respects to the natural product.

SUMMARY

Ecdysone is now available by three synthetic routes, each involving novel synthetic transformations. In addition to providing a source of the natural product, these syntheses provide an ecdysone-like skeleton that can be modified to determine those structural features of insect moulting hormones required for biological activity. Hopefully, this will lead to a thorough understanding of the structure-activity relationships of the insect moulting hormones in general.

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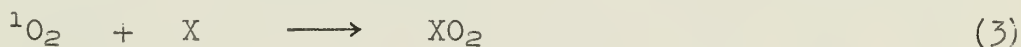
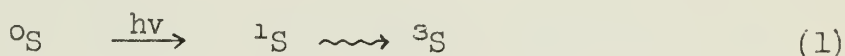
RECENT SINGLET OXYGEN CHEMISTRY

Reported by Thomas S. Woods

November 21, 1968


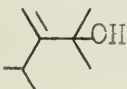
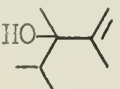

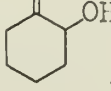
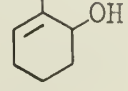
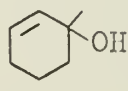

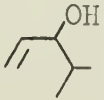
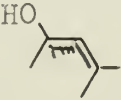
Photooxidation of organic molecules with molecular oxygen in the presence of dye sensitizers has received much attention in the recent literature. Evidence exists that the reaction proceeds via electronically excited oxygen in a singlet spin state as opposed to ground state oxygen in which electrons are unpaired. This singlet oxygen has been produced chemically and photolytically, and studies of oxygenations with singlet oxygen produced in both ways have been extensive. Several reviews¹⁻⁴ have covered the subject of reactions of singlet oxygen, and consequently this seminar will discuss only the most recent work done in the field. The mechanism of production of singlet oxygen will be discussed before considering the most recent literature.

The phenomenon of sensitized photooxidation may be considered in two different ways, each of which is consistent with the kinetic studies which have been done.⁵⁻⁷ The first mechanism, proposed by Kautsky in 1931,⁸ involved excitation of the sensitizer (⁰S) to the first excited singlet state (¹S), followed by intersystem crossing to the lowest triplet state (³S) (Eq. 1). This triplet then reacted with ground state triplet oxygen, a spin allowed process, to produce ground state sensitizer and excited singlet oxygen (¹O₂) (Eq. 2), which subsequently reacted with some acceptor (X) to give a peroxide (Eq. 3). The other mechanism, proposed by Schönberg⁹ in 1935, required that the excited triplet sensitizer first form a biradical complex with oxygen⁵ (Eq. 4) and that this complex then attack the acceptor to produce the peroxide (Eq. 5). Schönberg's mechanism was generally accepted until recent evidence revived Kautsky's singlet oxygen mechanism, which is currently favored by most workers.



Evidence that singlet oxygen is the attacking species in dye-sensitized photooxidations was provided^{1a} by comparing the product ratios in systems which can give more than one product with those obtained from oxidations by chemically generated singlet oxygen. The source of the chemically generated singlet oxygen was the reaction between sodium hypochlorite and alkaline hydrogen peroxide, a system which will be discussed later. The results of this comparison (Table I) show that the product ratios from the two methods are identical within experimental error.

Table I^{1a}
Products of Olefin Oxygenations
(After Reduction to the Alcohols)

Olefin	Alcohol A	Alcohol B	Photooxidation		OCl ⁻ /H ₂ O ₂	
			%A	%B	%A	%B
			40	60	39	61
	 , 		44, 20	36	44, 20	36
			96	4	94	6

The oxygen molecule has two excited singlet states, $^1\Delta_g$ and $^1\Sigma_g^+$, which lie 22 kcal and 37 kcal, respectively, above the ground state.¹ The electron configurations^{1,2} and postulated structures^{2,10} of these excited states are shown in Figure I.

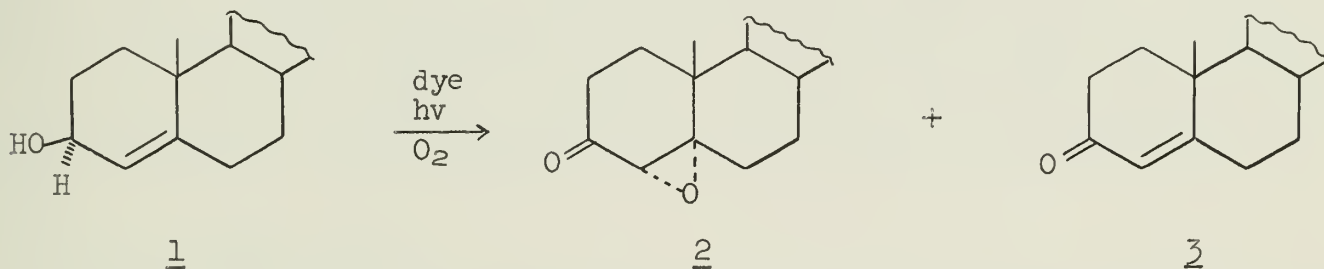
Figure I

Energy Level	Configuration of Highest Occupied Orbitals	Energy Above Ground State (kcal)	Postulated Structure
$^1\Sigma_g^+$	$\uparrow \quad \downarrow$	37	$\uparrow\ddot{O}-\ddot{O}\downarrow$
$^1\Delta_g$	$\uparrow\downarrow \quad \text{---}$	22	$\ddot{O}=\ddot{O}$
$^3\Sigma_g^-$	$\uparrow \quad \uparrow$	0	$\uparrow\ddot{O}-\ddot{O}\uparrow$

The lifetime of the $^1\Delta_g$ state is much greater than that of the $^1\Sigma_g^+$ state; the $^1\Delta_g$ state is able to survive 10^8 collisions with vaporous methanol, while the $^1\Sigma_g^+$ state can survive only ten such collisions.^{1b}

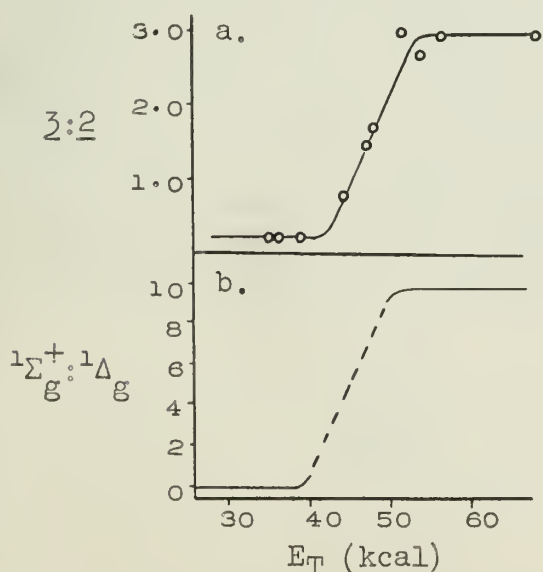
Solutions containing singlet oxygen are chemiluminescent, giving off a characteristic red glow.¹¹ The source of light emission is reportedly due¹⁰ to a bimolecular collision of two $^1\Delta_g$ oxygen molecules, collapsing to two molecules of ground state oxygen with light emission.

Evidence has recently been presented that both the $^1\Delta_g$ and the $^1\Sigma_g^+$ states are involved as oxidizing species in photooxidations. Kearns and his coworkers¹² studied the photooxidation of cholest-4-en-3 β -ol (1) in the presence of various dye sensitizers. System 1 had previously been studied extensively by Nickon and Mendelson¹³ who examined the stereospecificity of the reaction. The products of the photooxidation



were an epoxy ketone 2 and an α,β -unsaturated ketone 3. Kearns noted that as sensitizing dyes with increasing triplet energies were employed, the product ratio of unsaturated ketone to epoxy ketone, 3:2, also increased. A plot of the observed

Figure II



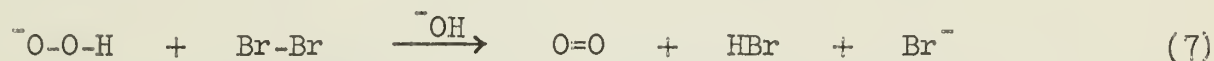
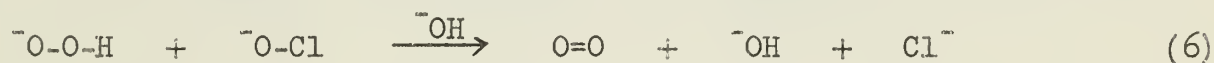
a. - Observed Ratio of 3:2 versus Triplet Energy of Sensitizer. b. - Predicted $^1\Sigma_g^+ : ^1\Delta_g$ Ratio versus Triplet Energy of Sensitizer.

3:2 ratio versus the triplet energy of the dyes employed gave the curve in Figure IIa. Plotting the predicted ratio of $^1\Sigma_g^+$ to $^1\Delta_g$ oxygen present versus the triplet energies gave the curve in Figure IIb. Noting that the curves were identical, Kearns suggested that the $^1\Sigma_g^+$ excited oxygen was responsible for the enone 3, while the $^1\Delta_g$ state led to the epoxy ketone 2. Further testing of this hypothesis prompted Kearns¹⁴ to investigate the concentration dependence of the 3:2 ratio. He reasoned that, since the $^1\Sigma_g^+$ state was so much shorter lived than the $^1\Delta_g$ state, a reduction in the concentration of 1 should also lead to a reduction in the 3:2 ratio, since the products formed should be mainly those arising from the longer lived $^1\Delta_g$ state. In support of this

hypothesis, Kearns presented data which did indeed exhibit the predicted trend. Foote^{1b,15} has challenged this interpretation, but the details of his dissent are still not clear.

PRODUCTION OF SINGLET OXYGEN

Singlet oxygen has been prepared in several different ways; sensitized photo-oxidation has previously been mentioned. Of the many chemical methods which have been used, the most important is the reaction of sodium hypochlorite and alkaline hydrogen peroxide,^{1,10,16} which presumably proceeds by the heterolytic reaction shown in Equation 6. Similarly alkaline solutions of bromine and peroxide yield singlet oxygen¹⁰ (Eq. 7). Other chemical methods for production of singlet oxygen



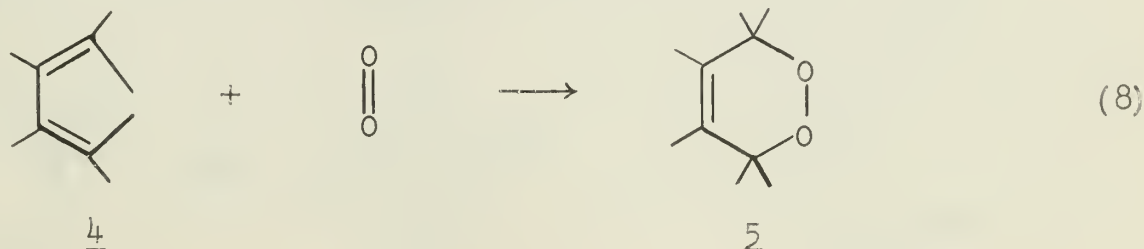
include¹⁰ the reaction of alkaline solutions of organic peracids with hydrogen peroxide, the reaction of alkaline hydrogen peroxide with nitriles, and the oxidation of formaldehyde by alkaline hydrogen peroxide in the presence of pyrogallol.

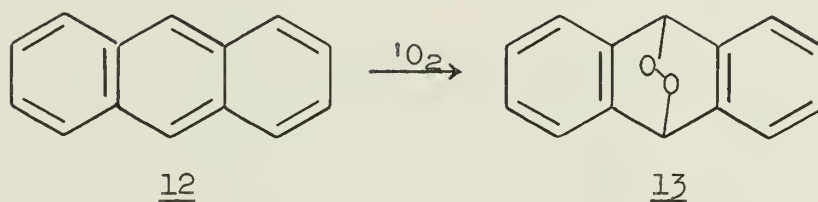
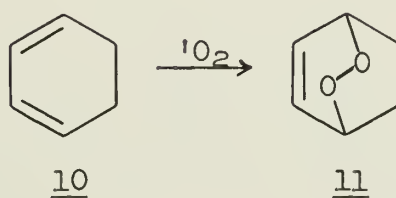
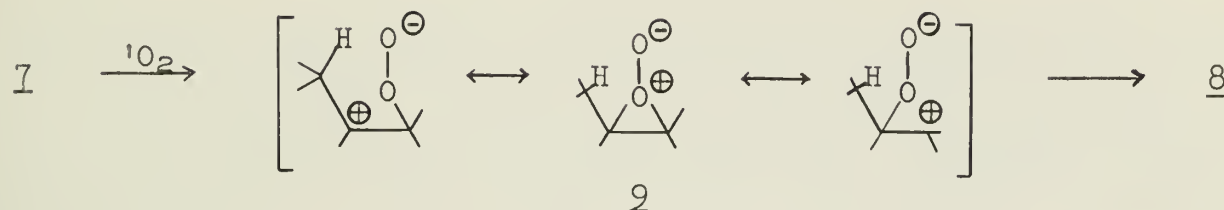
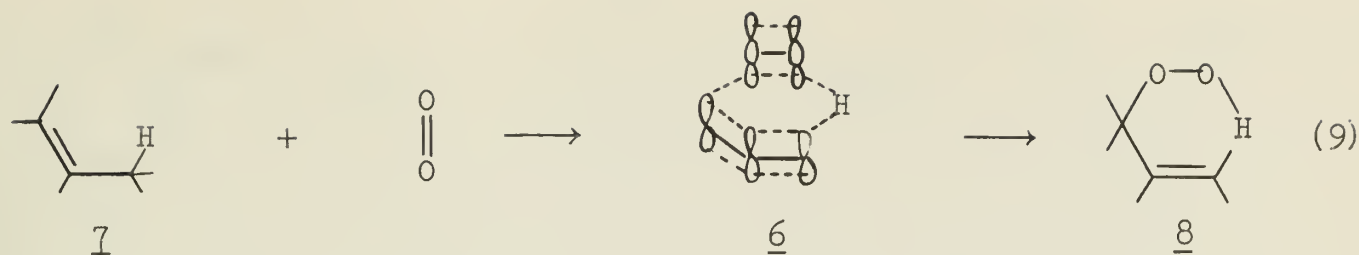
The thermal decomposition of photolytically produced peroxides of certain aromatic hydrocarbons, such as 9,10-diphenylanthracene endo-peroxide, has been reported¹⁷ to give singlet oxygen in good yield, as has the subjection of molecular oxygen to electrodeless discharge from a radiofrequency transmitter unit.¹⁸ Murray and Kaplan and associates^{19,20} have reported that singlet oxygen is produced by the thermal decomposition of the complex of triphenyl phosphite and ozone [(C₆H₅O)₃P·O₃]. They²¹ detected ¹Δ_g oxygen by carrying out the decomposition in the cavity of an epr instrument. It has been pointed out,^{1b} however, that the complex can react with acceptors at temperatures below those at which singlet oxygen is evolved. Also, the relative rate of oxygenation with triphenyl phosphite-ozone is apparently not identical with that using other methods of producing singlet oxygen; consequently, the exact nature of the oxygenating species in this case is still under question.

Since the product ratios of reactions of singlet oxygen with organic molecules have been shown to be identical regardless of the source of singlet oxygen,^{1a,16} the method of producing singlet oxygen will not be specified in the remainder of the seminar.

REACTIONS OF SINGLET OXYGEN

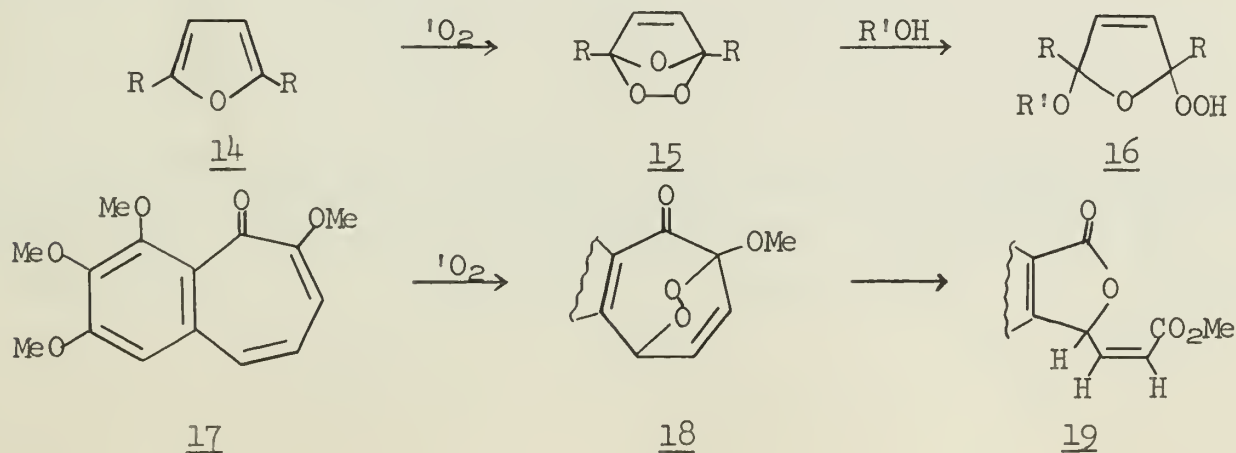
Reactions of singlet oxygen may be divided into two general classifications—those in which singlet oxygen reacts with dienes in a Diels-Alder type addition and those in which singlet oxygen acts as an ene in the Alder "ene" reaction. In the former (Eq. 8) a concerted cycloaddition of singlet oxygen to dienes (4) to form cyclic peroxides (5) has been postulated as the mechanism.¹⁰ In the ene-type addition (Eq. 9) the reaction presumably involves a cyclic transition state^{1a,3,22} 6 when an olefin with an allylic hydrogen atom 7 and singlet oxygen assume the required geometry. The product of the reaction is an allylic hydroperoxide 8 in which the double bond of the olefin has been shifted with abstraction of the allylic hydrogen. The reaction has been shown to be stereospecific¹³ in studies of steroidal olefins. The above mechanism is not the only one that fits the observed data, since a concerted cycloaddition of singlet oxygen to the olefin 7 to give 8 via the intermediate 9, as proposed by Nickon,²³ may not be ruled out.

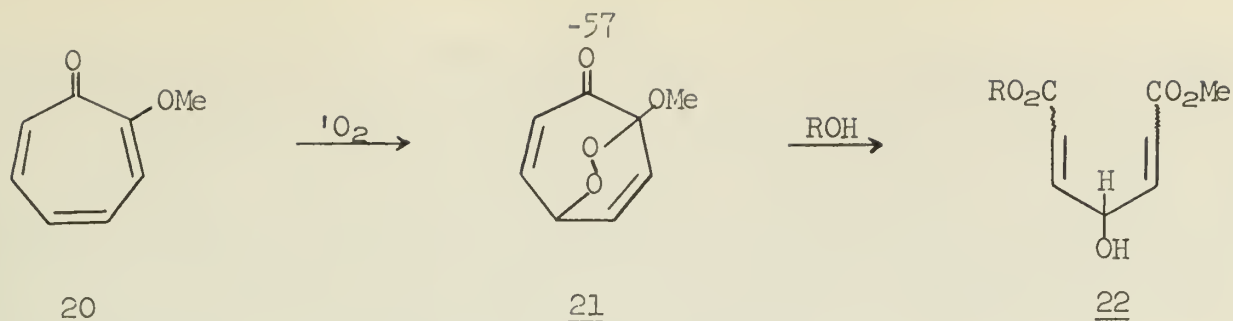




DIELS-ALDER TYPE ADDITIONS

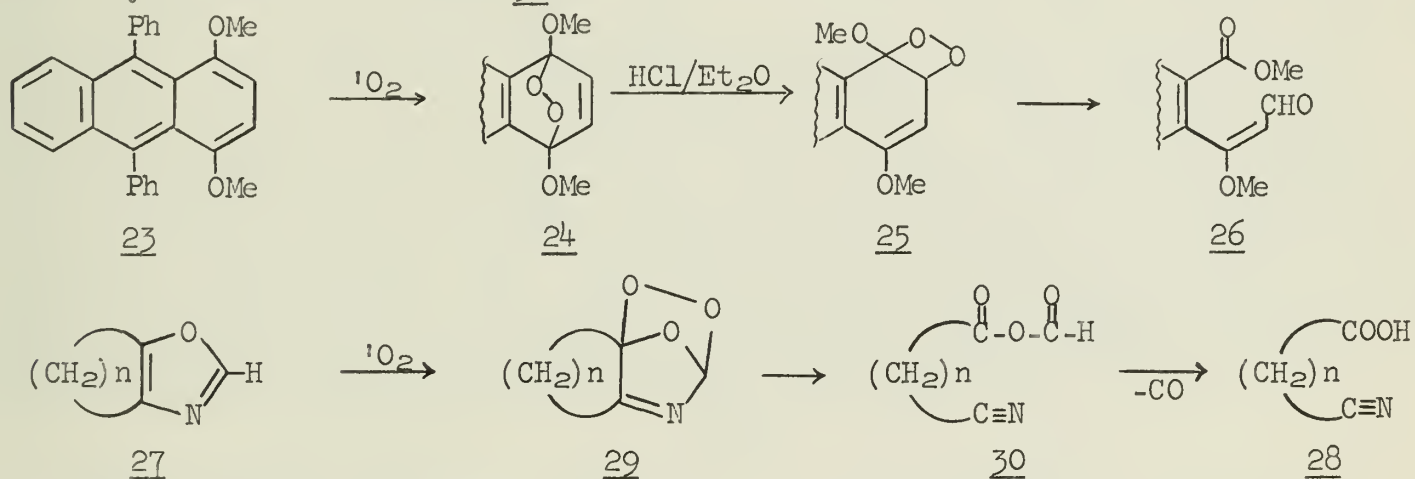
Some acceptors which add singlet oxygen in a Diels-Alder addition include cyclohexadiene, which reacts with singlet oxygen to give norascaridol (11),^{16,24} and anthracene (12) and related aromatic hydrocarbons, which give endo-peroxides 13 on exposure to singlet oxygen.^{1,7,10,16,25} Substituted and unsubstituted furans (14)²⁶ add singlet oxygen in a Diels-Alder addition to give isolable endoperoxides of type 15. The reaction is apparently general, even when the substituent forms a ring exocyclic to the furan ring. More recently reported reactions of this type include those of the photooxidation of tropolones. Forbes and Griffiths²⁷ caused tetra-*O*-methylpurpurogallin (17) to react with singlet oxygen to produce the transannular peroxide 18 which subsequently rearranged to the γ -lactone 19. The authors envisioned the mechanism of the rearrangement as a rupture of the peroxide bond of 18, followed by homolysis of the bond between the carbonyl carbon and the adjacent methoxide carbon, with formation of a carbonyl group on the methoxide carbon. The resulting diradical can ring close to give 19. Reaction²⁸ of 2-methoxytropone (20) with singlet oxygen gave the endo-peroxide 21, which could be isolated. The intermediate 21 was found to rearrange in solvents such as carbon disulfide to a lactone product analogous to 19, but in carbon disulfide/alcohol/ether, the diester 22 was formed, the alkyl group depending on the alcohol used.





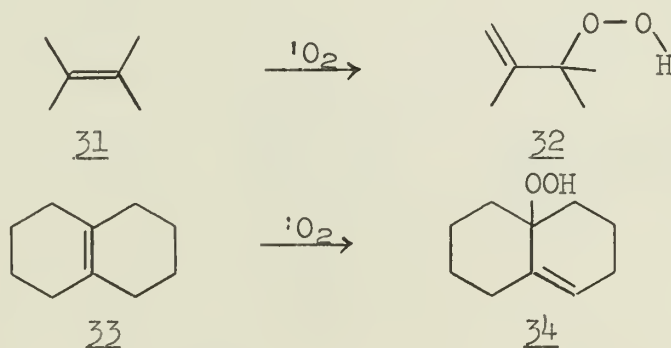
Baldwin, Basson, and Kraus²⁹ recently reported that certain aromatic nuclei, after reaction with singlet oxygen, may be cleaved by non-aqueous acid in a process which yields products similar to those formed in the biogenesis of certain natural products. As an example, they caused 1,4-dimethoxy-9,10-diphenylanthracene (23) to react with singlet oxygen to give the *endo*-peroxide 24. In ethereal hydrogen chloride, 24 presumably rearranged to the dioxetane 25 which then underwent ring opening to the aldehyde ester 26.

Wasserman and Druckrey³⁰ have recently observed a reaction which they suggest would be useful in the preparation of ω -cyano acids. 4,5-Exocyclic substituted oxazoles and singlet oxygen produced a normal ozonide-type intermediate which presumably underwent ring opening with loss of carbon monoxide to the cyano acid. Thus, oxazole 27 gave the cyano acid 28, passing through the oxygen adduct 29 and the mixed anhydride of formic acid 30.

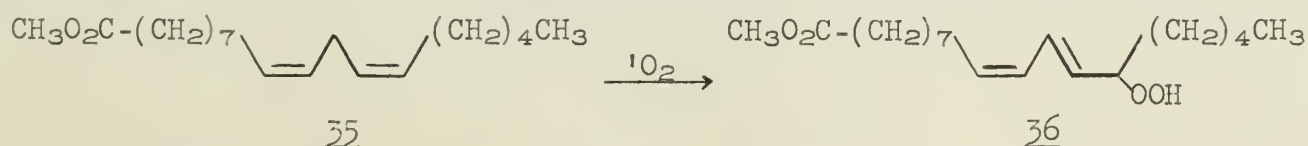


FORMATION OF ALLYLIC HYDROPEROXIDES

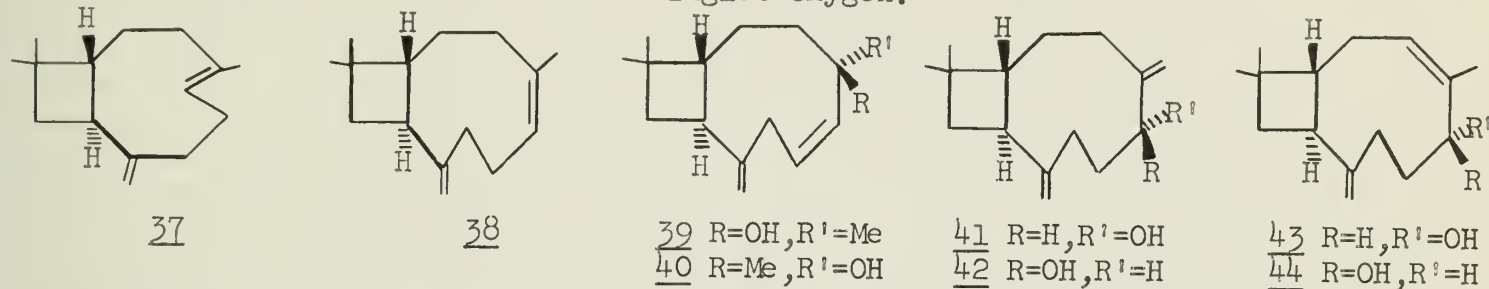
Some classic reactions of singlet oxygen with olefins include that of 2,3-dimethyl-2-butene (31) to give 2,3-dimethyl-3-hydroperoxy-1-butene (32),^{1a,16,24} and that of $\Delta^{9,10}$ -octalin (33) to give 10-hydroperoxy- $\Delta^{1,9}$ -octalin (34).^{1a,16,31}



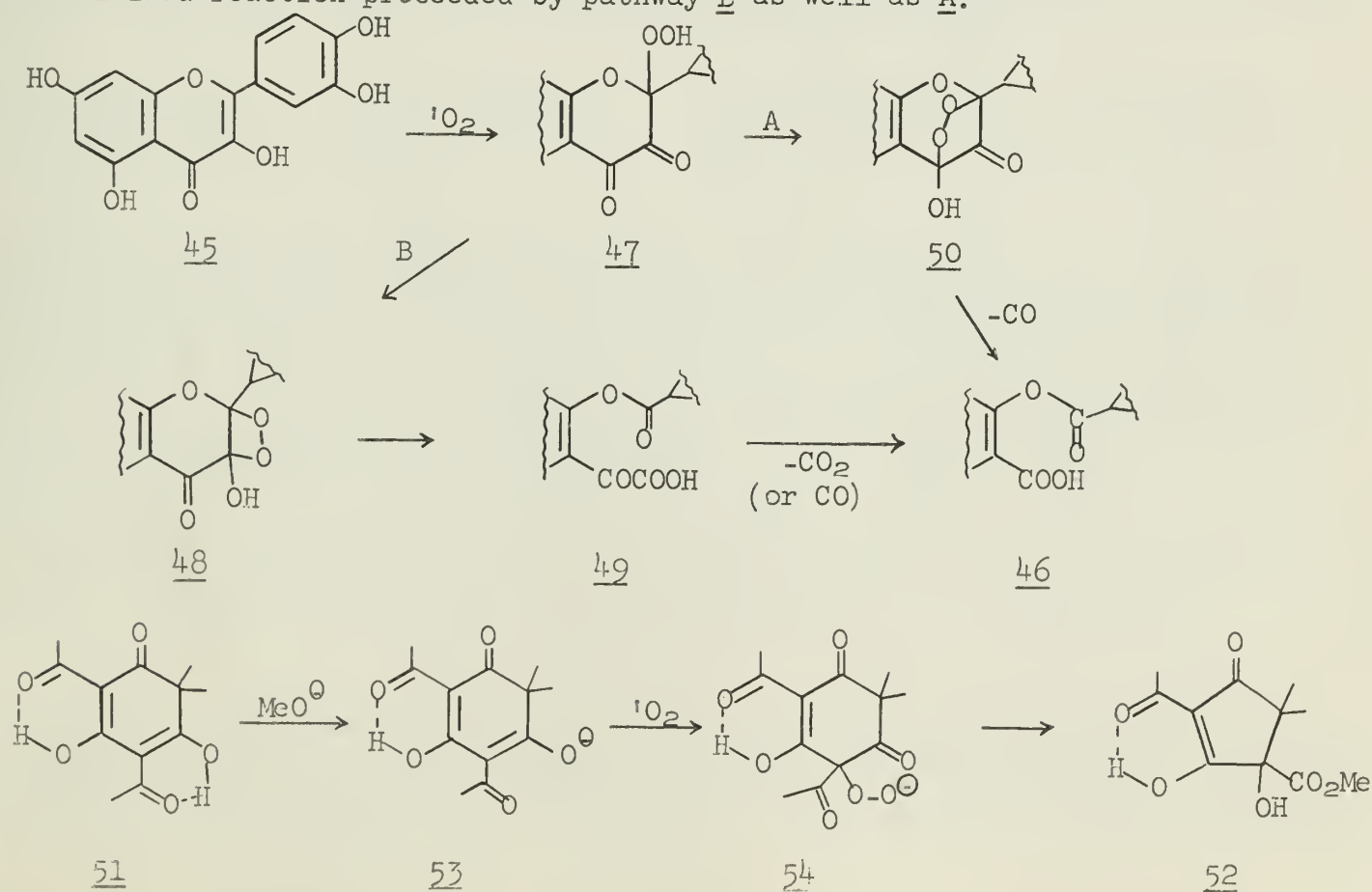
More recent studies of reactions of this type have included a report on the oxygenation of fatty acids by singlet oxygen.³² Methyl linoleate (35) reacted with singlet oxygen to give methyl 13-hydroperoxy-9,11-octadecadienoate (36).

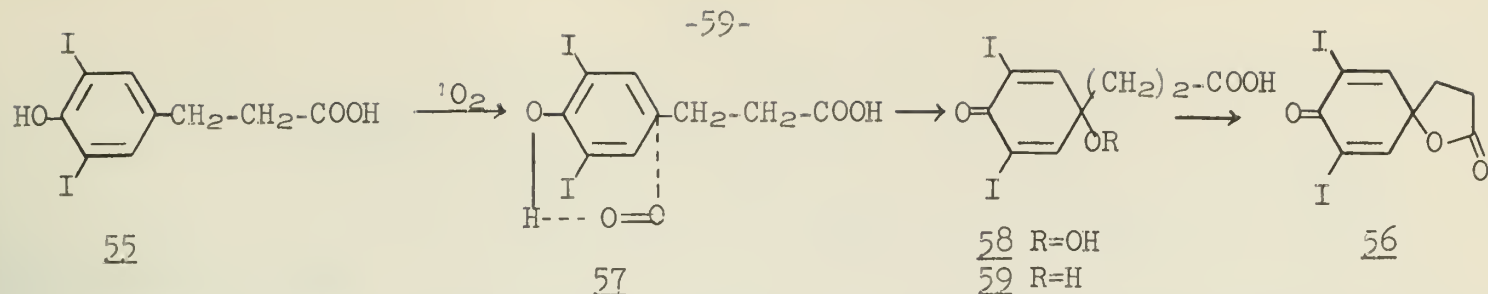


Schulte-Elte and Ohloff³³ have reported the dye-sensitized photooxidation of (-)-caryophyllene (37) and (-)-isocaryophyllene (38) to allyl hydroperoxides, which were identified by reduction to the allyl alcohols, 39-44. From the oxygenation of 37, compounds 41, 42, 43, and 44 were produced, while from 38, all six possible allylic alcohols were formed. Trace amounts of epoxide products were also noted. Similar results were reported by Gollnick and Schade,²² who studied the stereospecificity of the reaction. They suggested that the relative amounts of the products in the reaction were due to the relative amounts of the stable conformations of the starting materials available for the attack of singlet oxygen.



Matsuura and his coworkers³⁴ have observed a reaction of this type with 3-hydroxyflavones and singlet oxygen. This reaction is different from those previously mentioned in that the double bond shifts, not to carbon as is usually noted, but rather to the oxygen of a hydroxyl group with the formation of a carbonyl group. For example, quercetin (45) reacted with singlet oxygen to give an acidic ester 46. The first step in the reaction was apparently the addition of singlet oxygen to 45, forming the hydroperoxide 47. The authors then suggested two possible pathways, A and B, for the rearrangement to 46. By pathway B, 47 would rearrange to the dioxetane 48, which would then undergo ring opening to give the keto acid 49. Oxidative decarboxylation of 49 would give the observed product 46. By reaction path A, 47 would rearrange to the five-membered ring peroxide 50. Decarbonylation of 50 with ring opening would then give 46 directly. The two pathways were considered because, in photosensitized oxidations, carbon dioxide and carbon monoxide could be detected, while in biological oxidative degradations of the same type of compounds, carbon monoxide was noted. The authors speculated that the biological reaction proceeded via pathway A while the photosensitized reaction proceeded by pathway B as well as A.



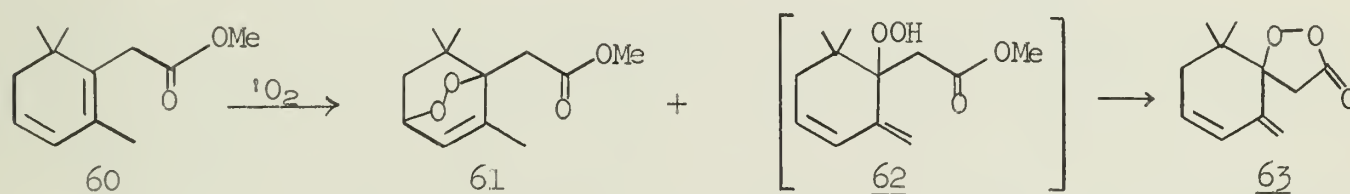


Young and Hart³⁵ reported that diacetylphilicinic acid (51) was inert to singlet oxygen in neutral solution, but that in excess sodium methoxide, 51 reacted with singlet oxygen to produce 52, a process which presumably also involved a double bond shift to oxygen. The authors proposed that attack of singlet oxygen on the enolate anion 53 led to the peroxide anion 54 which rearranged to 52. They provided evidence that singlet oxygen was the attacking species in the reaction by addition of Rose Bengal, a common sensitizer used to produce singlet oxygen, to the solution containing 53. With the dye present, the reaction was noted to give a 98% yield in thirty-five minutes, while with no dye, the reaction gave only a 4% yield in two hours. It was also reported that the same product 52 was isolated when 51 was heated under reflux in a methoxide solution containing 9,10-diphenylanthracene peroxide, conditions which have been reported to yield singlet oxygen.¹⁷

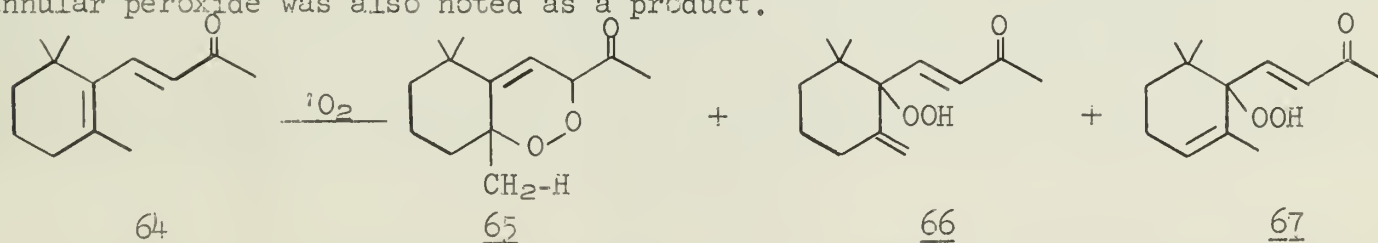
An unusual reaction of singlet oxygen in which a 1,6-addition rather than a 1,4-addition of oxygen is apparently involved was observed by Matsuura and his associates.³⁶ They found that 3,4-diiodophloretic acid (55) reacts with singlet oxygen to give the spirolactone 56. They suggested that the initial step in the reaction was the 1,6-addition of oxygen as is shown in 57, resulting in the hydroperoxide 58. Next, the peroxide function of 58 was reduced to hydroxide, giving 59, followed by normal lactonization to the spirolactone 56.

SYSTEMS WHICH UNDERGO BOTH MODES OF ADDITION

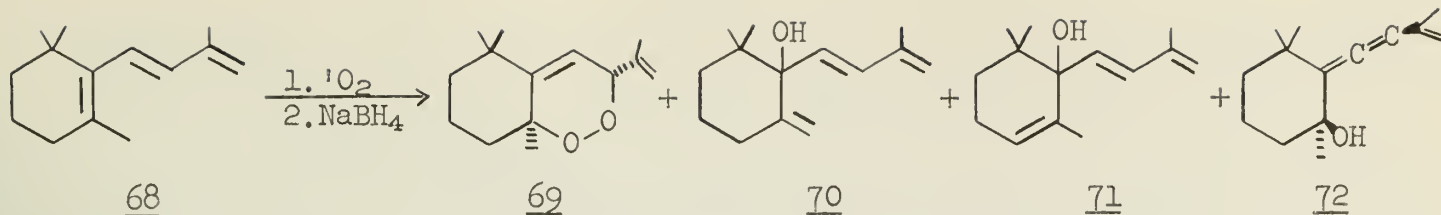
In the reactions of singlet oxygen with some dienoid systems, both the expected Diels-Alder adduct and the ene-type adduct are noted. An example of this type of addition was encountered by Demole and Enggist,³⁷ who caused methyl homosafranate (60) to react with singlet oxygen and obtained the endo-peroxide 61 and the hydroperoxide 62, which subsequently rearranged to the spiroperoxy lactone 63.



Another system that can undergo both modes of oxygen addition was studied by Mousseron-Canet and her associates,³⁸ who examined the sensitized photooxidation of β -ionone (64). From the photolysis they isolated a derivative of the normal Diels-Alder adduct 65 along with the alcohol derivatives of two hydroperoxides 66 and 67. Results similar to these were reported by the same workers³⁹ in their study of the reaction of methyl dehydro- β -ionylidene acetate, except that an additional trans-annular peroxide was also noted as a product.

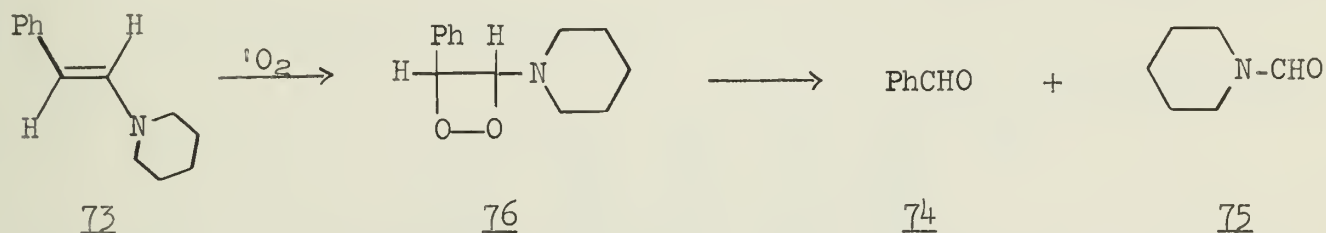


Footo and Brenner⁴⁰ noted an interesting compound in their study of the reaction of a similar system with singlet oxygen. 3-Methyl-1-(2,6,6-trimethylcyclohexen-1-yl)-1,3-butadiene (68) gave not only the Diels-Alder adduct 69 and ene adducts 70 and 71, but also the allenic product 72.



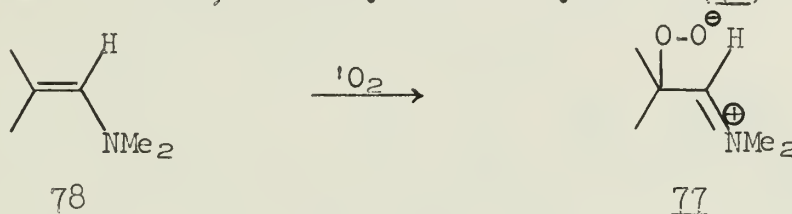
OTHER REACTION TYPES

Enamines undergo interesting reactions with singlet oxygen to produce two carbonyl fragments from the two carbons originally involved in the double bond. Foote¹ reported the reaction of 1-phenyl-2-piperidinoethylene (73) with singlet oxygen to give benzaldehyde (74) and N-formylpiperidine (75), probably by way of the 2 + 2 cycloadduct 76. A similar mechanism has been advocated by Huber⁴¹ in his studies of



steroidal enamines. Foote⁴² observed in a later communication that the nmr spectra of the adducts were temperature dependent and at low temperatures were much more complex than one would predict for a simple cycloaddition product of type 76; consequently, he suggested that perhaps a dimer was present.

Another mechanism which has been considered by Foote⁴² and by Matsuura and Saito⁴³ is the formation of a zwitterionic intermediate such as 77 which might be encountered in the reaction of N,N-dimethyl isobutenylamine (78) with singlet oxygen.



Wasserman and his associates⁴⁴ investigated the reaction of singlet oxygen with imidazoles and found that tetraphenylimidazole gave N,N'-dibenzoyl-N-phenylbenzamidine on reaction with singlet oxygen. Others have reported⁴⁵ the reaction of pentaphenylpyrrole with singlet oxygen to give a variety of products.

Photolysis of 2,5-dioxolanes in the presence of oxygen has been reported^{46,47} to yield interesting products; however, no claim for singlet oxygen intermediacy was made, and the reaction does not fit any mechanism which is generally accepted for a singlet oxygen reaction. The reaction probably proceeds by a radical addition of oxygen. Dye sensitization studies of the reaction should be informative.

CONCLUSION

Singlet oxygen has become a valuable synthetic tool and shows promise of even greater utility, especially in natural product synthesis. The mechanism of its reaction with organic molecules, although fairly well understood, still needs clarification, particularly in the area of enamine photooxidation. The resolution of the question of the participation of both excited singlet states in oxygenations should provide further insight into the mechanism.

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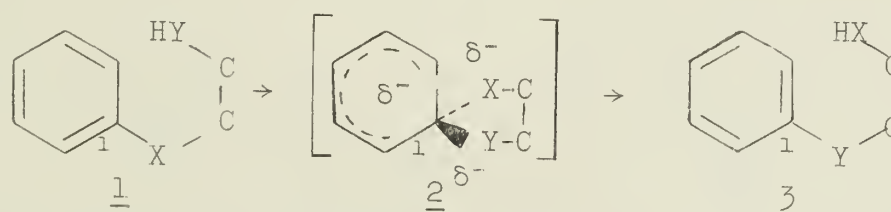
THE SMILES REARRANGEMENT

Reported by Richard M. Forbis

November 25, 1968

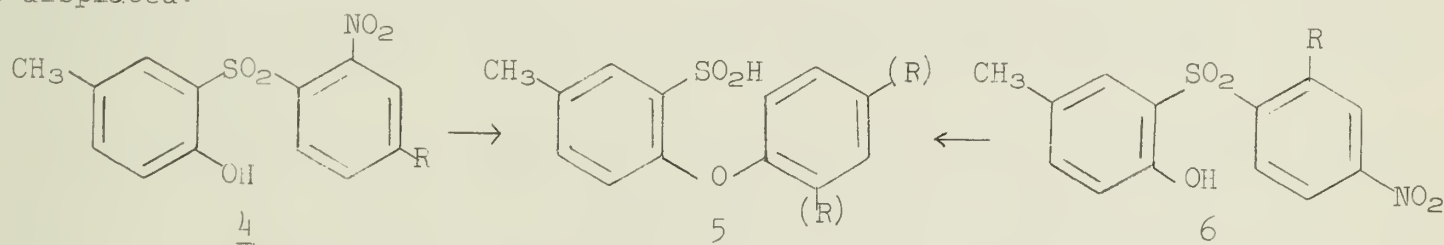
A class of reactions which are, in effect, intramolecular nucleophilic aromatic substitutions resulting in the migration of an aromatic system from one heteroatom to another is known collectively as the Smiles rearrangement. A thorough review of the early work on this rearrangement, chiefly by Samuel Smiles himself, was published in 1951;¹ this seminar will summarize the significant advances that have been reported subsequent to this review, with emphasis on mechanism and synthetic utility of the rearrangement.

Represented schematically as the conversion of 1 to 3, the Smiles rearrangement is generally postulated to involve ionization of the YH functionality to the anion Y^- , followed by nucleophilic displacement of the X moiety through attack of this anion on the C-1 carbon of the aromatic nucleus involving a transition state similar to 2. Thus, this rearrangement must be considered on the basis of (1) substituent effects on the aromatic ring, (2) the nature of the bridge between X and Y, (3) the nature and effects of variation of X and Y, and (4) the effect of catalysis on the reaction.

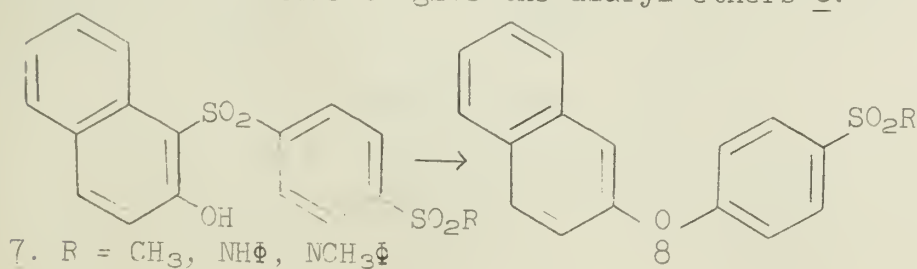


SUBSTITUENT EFFECTS ON THE AROMATIC RING

Of the several factors governing the rate of these rearrangements, activation of the carbon atom at which substitution occurs is most easily isolated. Few rearrangements of this type occur without some kind of activation in the aromatic ring of 1. The first extensive investigation of the effect of activation on the Smiles rearrangement was carried out by Galbraith and Smiles, who studied the effect of substitution in the alkali-catalyzed rearrangement of sulfones 4 and 6 to the corresponding ethers 5.² Both series of derivatives showed the following order of reactivity: $NO_2 > COPh > COO^- > Cl > H$, indicating substituent activation by increasing the positive character of the carbon atom from which the sulfonyl group is displaced.

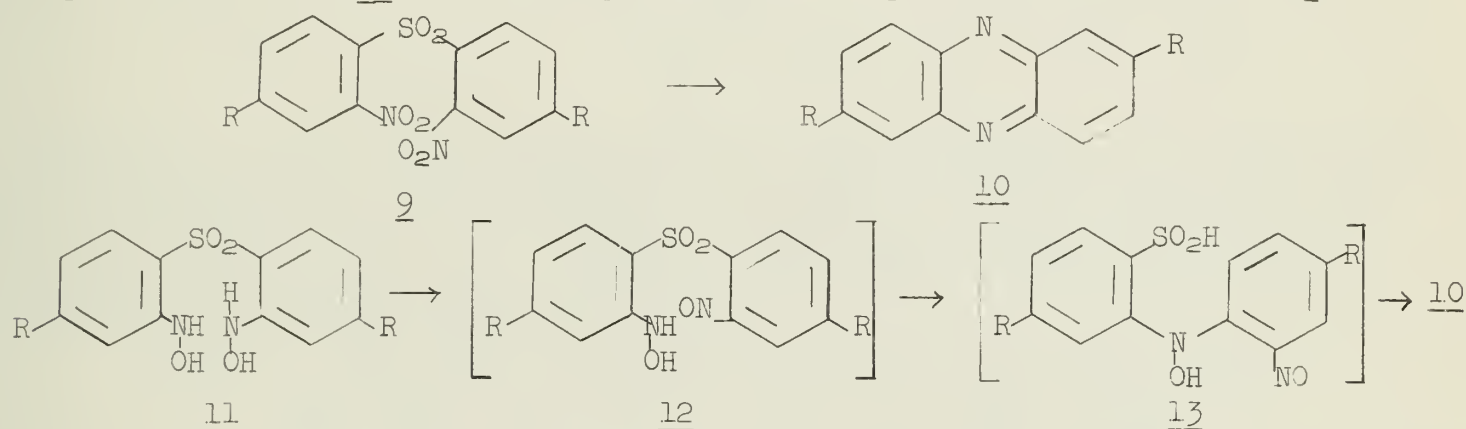


In studying activation by groups other than the strongly electron-withdrawing nitro group, it was found that the methanesulfonyl and sulfonamide groups provide adequate activation to permit the rearrangement of 7.³ However, in contrast to the relatively mild conditions under which the nitro-activated sulfones 4 and 6 rearranged (1.25 equiv. $NaOCH_3$, 0° and 50°), these compounds require heating to 150° in the presence of base, under which conditions the rearranged naphthyl sulfinic acids lose sulfur dioxide to give the diaryl ethers 8.



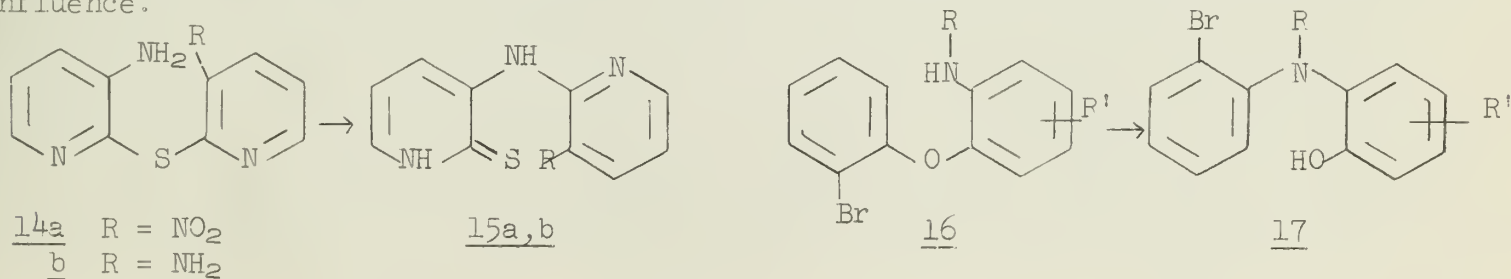
A recent investigation into the mechanism of the formation of phenazines 10 by the zinc-alkali reduction of 2,2'-dinitrodiaryl sulfones 9 has suggested a Smiles rearrangement activated by the nitroso group.^{4,5} Although intermediates

in the conversion of 9 to 10 have not been isolated, the treatment of the corresponding hydroxylamino derivatives 11 with base gave products similar to the reduction of 9. In alkali at room temperature, compounds such as 11 are postulated to undergo intermolecular disproportionation (as well as intramolecular) to give an intermediate nitroso derivative 12 which is suitably activated to rearrange in the Smiles manner to 13. Earlier investigations had indicated that a Smiles rearrangement at room temperature normally requires activation by at least two substituents, one of which must be the nitro group. The facile conversion in the present system has been attributed to the following factors. The nitroso group ortho to the position of nucleophilic attack exerts a strong electron-withdrawing influence; although little has been reported concerning activation by nitroso substituents toward nucleophilic substitution, this group is suspected to be more electron-withdrawing than the nitro group.⁶ In addition, the participation of the hydroxylamino group as the nucleophile may be particularly effective in promoting the rearrangement since the transition state involving the nucleophilic nitrogen can be stabilized by electron donation from the adjacent oxygen atom (the alpha effect).⁷ Formation of phenazines from the rearranged intermediate 13 would then proceed with ring closure and loss of SO₂.



In studying the reactions of 3,3'-diamino-2,2'-dipyridyl sulfide, 14b, Rodig and coworkers were able to observe the change in activation brought about by the substitution of an amino group for a nitro group, 14a, a conversion which should deactivate the system for rearrangement.⁸ It was found that the conversion of 14b to 15b proceeded smoothly in 10% HCl, although slower than the mono-nitro analog 14a. It was suggested that protonation of one of the amine groups might occur, negating its deactivating influence. However, a more complete study of the rate of rearrangement in relation to the pH and the effect of other substituents on this system has not been reported.

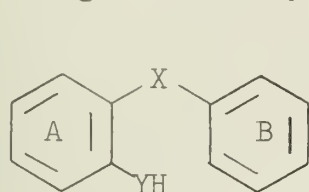
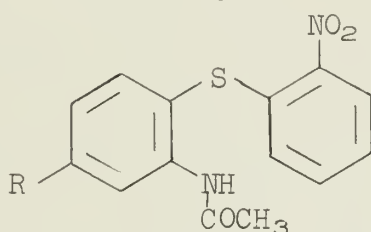
As illustrated by the conversion of 16 to 17, the Smiles rearrangement activated by halogen substituents has been independently investigated by several workers.^{9,10} In contrast to activation by the predominantly resonance effects of the *o*- and *p*-nitro groups, these halogen substituents must promote rearrangement mainly through inductive influence.



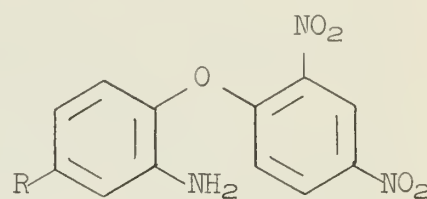
THE NATURE OF THE BRIDGE BETWEEN X AND Y

If an aromatic system provides the bridge between X and Y, as in 18, the effect of substitution in both aromatic rings must now be considered. The effect of substituents introduced into ring A is not as easy to predict as in the case of substitution in B, as electronic forces in A influence both X and Y. With respect to X, electron-withdrawing groups should promote the reaction by helping to stabilize the developing negative charge on X, and the effect should be strongest with substituents in the

4- and 6-positions. An ambiguity arises with the substituent effects on Y, depending upon whether YH is more or less acidic than the optimum for rapid rearrangement. If YH is insufficiently acidic, electron-withdrawing groups should assist the ionization of YH to Y^- ; however, a negative effect would be anticipated in the same system if YH is too acidic, resulting from insufficient nucleophilic activity of Y^- . As expected, substituents in the 3- or 5-positions should exert the strongest influence on Y. The rearrangement of the sulfide 19a, which occurred more rapidly than the rearrangement of the mono-nitro derivative 19b, illustrates the assistance of the electron-withdrawing group in the 4-position of the A ring.¹¹ It is postulated that the nitro group exerts its influence by increasing the ability of the sulfur to act as a leaving group and by increasing the acidity of the amine moiety.

18

19a, R = NO₂
b, R = H

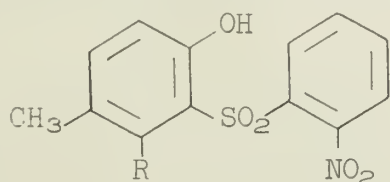
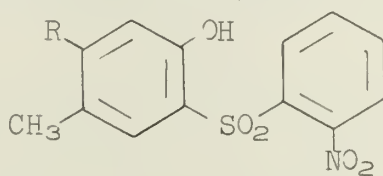
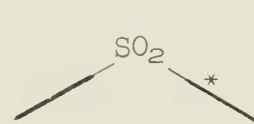
20

The effect of substitution of the A ring in the rearrangement of the amino-ether derivatives of 20 has also been investigated.¹² Table I lists the time required for complete rearrangement of each derivative, and indicates a distinct maximum in the rate of rearrangement when R = H. Arranged in the order of decreasing negative inductance, Table I suggests that optimum conditions for the reaction occur when R is a substituent with medium inductive effect.

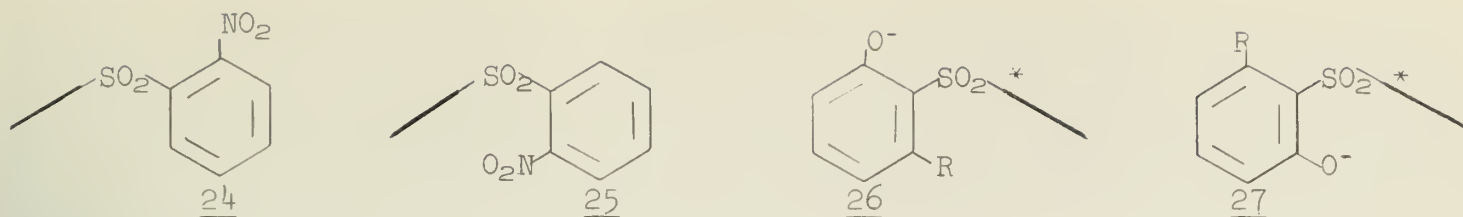
Table I. Rearrangement Times for Substituted Amino-ethers (20)

	NH ₂	OCH ₃	CH ₃	H	I	Br	Cl	COOAr	COOH
Time (min)	50	13	7	5	15	30	60	∞	∞

An early report by Smiles on the rearrangement of 2-hydroxy-2'-nitrodiaryl sulfones, 21, indicated that this reaction was greatly accelerated by a methyl group in the 6-position of the A ring.¹³ A careful study by Okamoto and Bunnett was undertaken to reveal whether this acceleration was due to a steric or electronic effect.^{14,15} Assuming that this rate increase with methyl substitution is actually due to steric rather than electron-donation effects, then relatively large substituents of opposite electronic effect in the 6-position would also be expected to accelerate the reaction. A kinetics study on the rearrangement of 21 and 22 indicated that the 6-substituted isomers 21, with both electron-withdrawing and electron-donating substituents, rearrange approximately 500,000 times faster than isomers 22. An interpretation of this large accelerating effect was suggested with reference to the five extreme conformations accessible to the sulfone molecule, 23-27, a straight representing a phenyl ring perpendicular to the plane of the paper, and an asterisk indicating the position of the C-1 carbon which must be attacked by the ionized hydroxyl group to allow rearrangement. In analogy to the mechanism of other nucleophilic aromatic substitution reactions, it is apparent that conformations resembling 27, in which the ionized hydroxyl group is brought laterally against the C-1 carbon atom, are prerequisite to rearrangement. Thus, qualitatively, an increase in the

21, R = CH₃, Cl, Br22, R = CH₃, Cl, Br23

bulk of the 6-substituent, R, should reduce the population of conformations resembling 26, with a corresponding increase in the probability of the necessary molecular conformation, leading to an increased rate of reaction.



THE NATURE OF X AND Y

In considering the mechanism of this intramolecular nucleophilic aromatic substitution, the basic factors governing the rearrangement, in addition to activation of the aromatic ring, include (1) the nucleophilicity of Y, (2) the tendency of YH to ionize in the medium used (for in most cases the anionic form Y^- is the attacking nucleophile), and (3) the character of X or its ability to serve as a leaving group in the rearrangement. These influences must be discussed with respect to each other, and also with respect to the sort of bridging unit which connects X and Y.

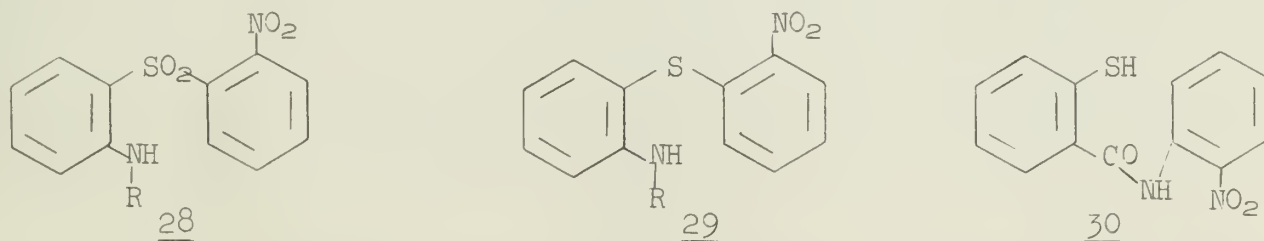
From the results of the early work of Smiles, it is apparent that in molecules provided with adequate activation, rearrangement would or would not occur depending on the nature of the groups X and Y. This early work of Smiles has been combined in Table II with investigations of later workers to provide a summary of the general classes of these rearrangements.^{1,9,16,17,18} This table indicates that rearrangement occurs most generally with more easily replaceable X groups (e.g., SO_2 and SO) and YH groups which are more nucleophilic in their anionic forms

Table II. Combinations of X and YH Suitable for Rearrangement

If YH is:	X may be:
NH_2 (aryl bridge)	$SO_2, O;$ not S, NH
NHacyl	SO_2, SO, S, O
$CONH_2$	SO_2, S, O
SO_2NH_2	O
SO_2H	O
OH (aryl bridge)	$SO_2, CO_2, SO_3, O;$ not SO, S
OH (alkyl bridge)	$SO_2, SO;$ not S
SH	O

According to the mechanism proposed by Smiles for the rearrangement of N-substituted amino-sulfones 28, the first step is conversion by base of the amino group to its anionic form followed by nucleophilic attack on the C-1 carbon atom.¹¹ Since the nucleophilic activity of the nitrogen diminishes as the acidic character of the group increases, it was expected that two classes of N-substituted derivatives would hinder rearrangement: those which decreased the acidity of the NH group sufficiently to hinder formation of the nitrogen anion and those which increased the acidity sufficiently to yield only a weakly nucleophilic anion. In a series of derivatives

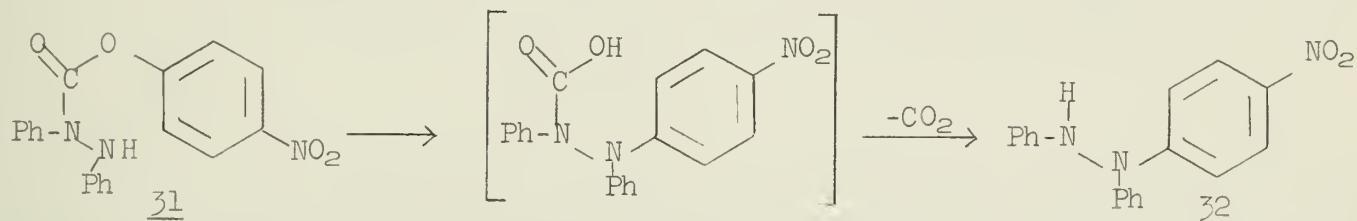
of increasing acidity, 28, $R = CH_3, H, CH_3CO, PhSO_2$, appreciable reactivity did not occur at either extreme. The N-methyl derivative rearranged more slowly than the parent amine, presumably due to insufficient acidity of the amino group. However, acylation of the amino group with an acid of moderate strength was found to aid the intramolecular rearrangement, while acylation with a strong acid (benzenesulfonic acid) had a negative effect.¹⁹ It was concluded that acylation would generally promote the rearrangement by increasing the acidity of the amino proton, unless the acylamino group forms a stable ion and reduces the nucleophilicity of the nitrogen.



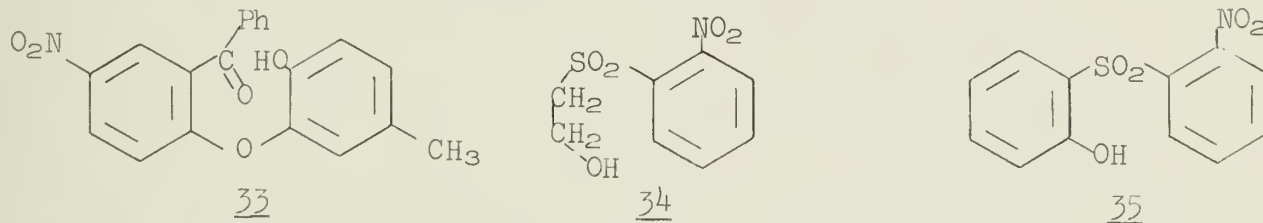
A similar study on the effect of N-substitution of amino-sulfides 29 also demonstrated that successful rearrangement of 29 depends upon the proper balance of the acidity and nucleophilicity of the nitrogen.¹¹ Derivatives of 29 in which R was methyl and hydrogen were found not to rearrange, illustrating insufficient acidity to allow ionization of the amino group. Normal base-catalyzed rearrangements of 29 were observed when R was acetyl and o-nitrobenzoyl, in contrast to unsuccessful attempts when R was benzenesulfonyl in which the amido anion was easily

formed but lacked the nucleophilic activity to successfully attack the C-1 carbon. In contrast with the inactivity of 29, R = H, the mercaptobenzamide 29 (CONH₂ instead of NHR) was found to rearrange smoothly to the expected anilide 30, again indicating that acylation of the amino group with a moderate strength acid favors rearrangement.²⁰ (The above conclusions, however, are derived from experiments in dilute alkali solution; a different point of maximum reactivity would be expected if a more strongly basic medium were employed.)

A new type of Smiles rearrangement was reported by Baudet and coworkers, 31 → 32, in which X = O, Y = NPh, and the carbon portion of the bridge adjacent to Y is replaced by nitrogen.¹⁶ The nitro group situated *para* to the phenoxy function and the acidity of the NPh group are the principal influences in this conversion, although the steric effect provided by the phenyl residue situated on the nitrogen atom adjacent to the carbonyl moiety also would be expected to increase the rate of the reaction (similar to the effect of the 6-methyl group on the A ring mentioned above).

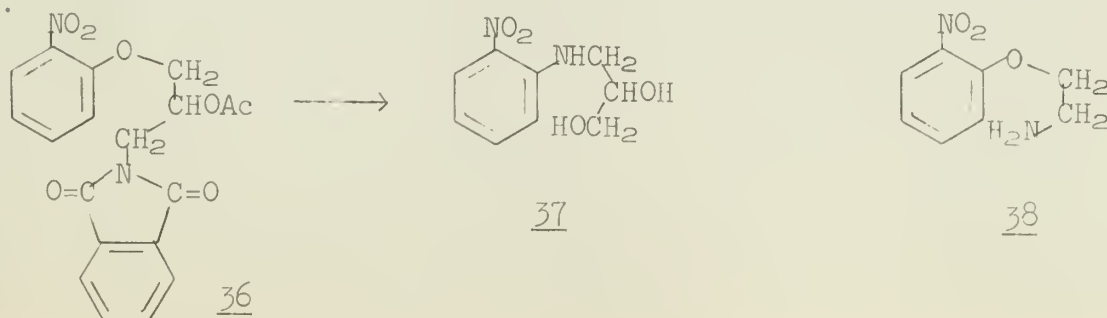


In these examples as well as those included in Table II, it has been shown that the different electron-donation capacities in dissimilar heteroatoms X and Y are an important factor governing the success of the rearrangement. The requirement of different nucleophilic capacities is also satisfied if X and Y are the same heteroatom but dissimilarly situated in the molecule, as in 33, which was found to rearrange almost quantitatively to the 4-methyl isomer.¹⁸



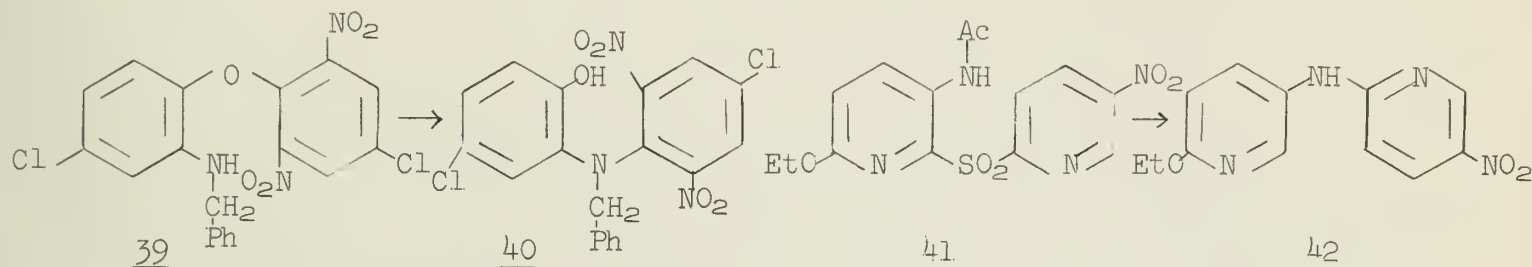
The most extensively investigated examples of the Smiles rearrangement have been those in which the groups X and Y are connected with an aromatic bridge (phenyl, naphthyl, or heterocyclic²¹). However, some interesting cases have been reported in which the bridge from X to Y is acyclic. Kent and Smiles found that the sulfone 34, containing an aliphatic hydroxyl group and C-1 carbon in a favorable 1,5-position, rearranged so rapidly that measurement of the reaction time by colorimetry was not possible.²² A similar result was observed with the base-catalyzed rearrangement of the sulfoxide corresponding to 34 (SO instead of SO₂), illustrating an activating influence of the aliphatic bridge over the aromatic bridge in 35.

Caldwell and Schweiker observed the rearrangement of the phthalimide 36 to 37 upon treatment with aqueous hydrazine in basic medium.¹⁷ This was the first example of an amino group on an alkyl side chain displacing an alkoxy group in the Smiles manner, as well as the first displacement reported in which the intervening carbon chain was more than two units in length. Preliminary evidence for a similar rearrangement of the homologous amine 38 to the corresponding anilino-ethanol has also been reported, but a publication in greater detail is needed to confirm this conversion.



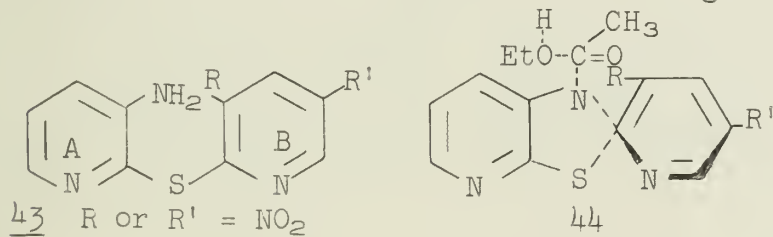
CATALYSIS EFFECTS

In almost all previous reports, the Smiles rearrangement has occurred under basic conditions, and it was thus postulated that the initial step of the reaction involves removal of a proton from YH to give the anion Y^- , which then acts as the attacking nucleophile. This assumption was supported by relative rate data for the rearrangement of hydroxy-sulfones similar to 4, in which it was found that an increase in the concentration of aqueous sodium hydroxide facilitated the conversion, as did going from weaker to stronger bases-- $\text{NaOH} < \text{NaOCH}_3 < \text{NaOC}_2\text{H}_5 < \text{NaOCH}(\text{CH}_3)_2$.²² The use of a basic solvent, pyridine, has also been reported to effect the conversion of 39 to 40.²³



Since it is known that protonation of the ring nitrogen in pyridine derivatives increases the ease of nucleophilic substitution, it is not unexpected that the Smiles rearrangement of dipyridyl derivatives would also be acid-catalyzed.²⁴ Maki and co-workers have reported several examples of acid-catalyzed rearrangements while trying to remove the acetyl group of the dipyridyl sulfone 41 in 35% HCl, obtaining the dipyridylamine 42.²¹

An earlier study revealed that amino sulfides 43 rearranged smoothly with 5% HCl in ethanol, and that the rate of conversion increased in more concentrated acid solutions.²⁵ The corresponding N-acetyl derivatives also underwent rearrangement in 5% HCl, but at a slower rate, to give only deacetylated products. These data suggest several interpretations: (1) the loss of the acetyl group may be necessary before rearrangement can occur; (2) the amides rearrange more slowly than the amines, followed by rapid solvolysis of the product; or (3) a concerted process occurs involving synchronous deacetylation and rearrangement having a transition state such as 44, aided possibly by protonation of the amide carbonyl moiety. There is, however, insufficient evidence available to distinguish among these mechanisms.



The catalyzing effect of acid in these dipyridyl systems has been explained by the protonation of either of the two ring nitrogen atoms, either increasing the susceptibility of the C-1 carbon to nucleophilic attack (protonation of B) or enhancing the ability of

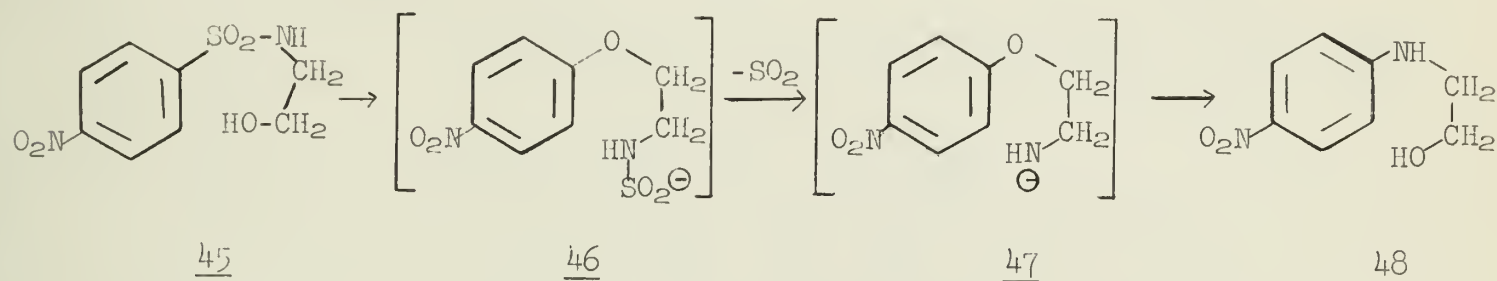
the sulfur atom to accommodate a negative charge (A ring protonation). Protonation of the A ring would also be expected to affect adversely the nucleophilic character of the amino group, as would direct protonation of the nucleophile itself.

Several examples have also been reported in which a Smiles-type rearrangement occurred under thermal conditions without the aid of acid or base. The first reported examples of this type detailed the conversion of *o*-aminodiaryl ethers to the corresponding hydroxyamines.²⁶ Rodig and coworkers observed that, in contrast to the acid-catalyzed reactions, the acetylated amino-dipyridyl sulfides 43 rearranged considerably faster than the non-acetylated derivatives when heated in ethanol.²⁵ When it was found that these acetylated derivatives rearranged more slowly in water than in ethanol, and not at all in benzene, a mechanism involving solvent participation was strongly suggested. In one possible mechanism the solvent can initiate the reaction by attack at the amide carbonyl with simultaneous release of an electron pair for attack at the C-1 carbon, such as 44. Since initial attack is not possible in the absence of a Lewis base or with the non-acetylated derivatives, rearrangement is less favored in these cases. Another possible mechanism

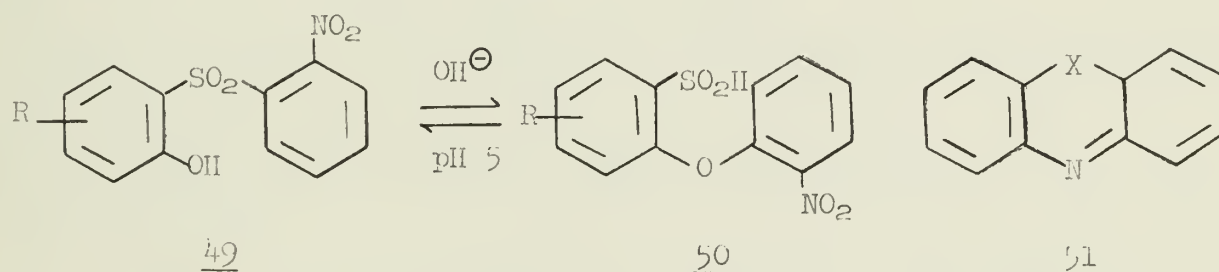
involving solvent-aided ionization of the amide proton is not consistent in view of the relative reaction rates of rearrangement in ethanol and water (water is considered to have a stronger ionizing power than ethanol) and the fact that no rearrangement occurred when 43 was heated in dimethylsulfoxide, an aprotic solvent of high ionizing ability.

VARIATIONS OF THE SMILES REARRANGEMENT

An interesting reaction which can be termed a "double" Smiles rearrangement has recently been reported by Kleb, who observed the conversion of a number of hydroxy-sulfonamides of basic structure 45 to the hydroxy-aniline compounds 48 in hot dilute NaOH solution.²⁷ Hydroxyalkyl amides similar to 45 whose hydroxyl group was either not in the β -position or sterically hindered would not react. A mechanism was suggested which was consistent with these observations in which, from an intermediate, 46, formed by Smiles-type rearrangement, a molecule of sulfur dioxide is eliminated to give 47. This 2-aminoalkylaryl ether can rearrange further under the influence of base to yield the N-(2-hydroxyethyl)aniline. Support for this mechanistic sequence is provided by the observation that ethers such as 47 rearrange immediately under the conditions employed. Thus, in this unique case, the atoms are restored to their original order after the loss of one molecule of sulfur dioxide by two intramolecular nucleophilic substitutions.

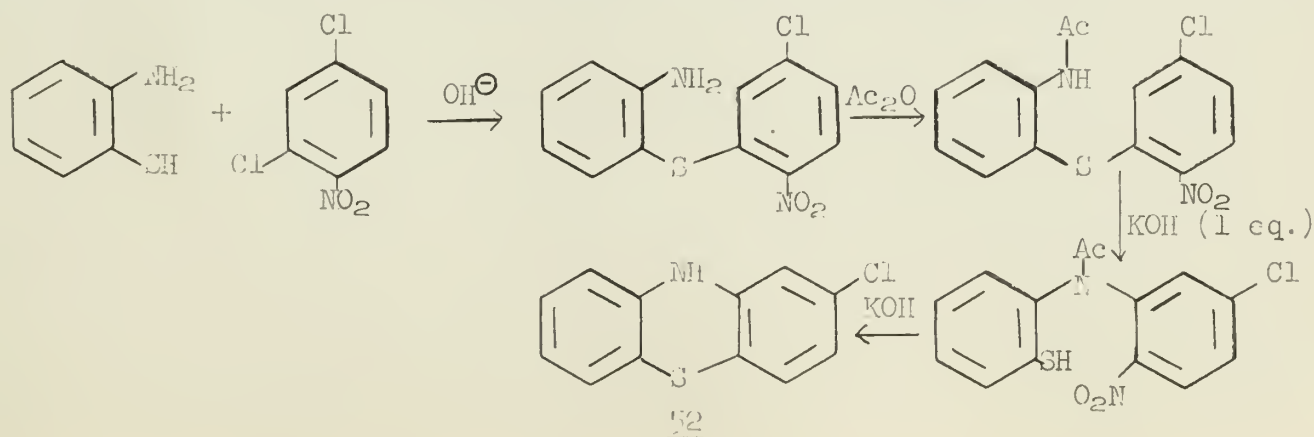


Another variation of the Smiles rearrangement has been noted in that many of the sulfinic acids 50 prepared by base-catalyzed rearrangement of *o*-hydroxysulfones 49 were capable of rearranging back to the original sulfones.¹³ These reverse Smiles rearrangements occurred at low pH (pH 2-6), under which conditions the sulfinic group but not hydroxyl group is in the ionized form.



SYNTHETIC APPLICATIONS

The wide versatility of the Smiles rearrangement becomes readily apparent when these reactions are applied to the syntheses of phenazines (51, X = N), phenothiazines



(51, X = S), phenoxazines (51, X = O), and their derivatives. In the continued interest in the relationships between the chemical structure of these heterocycles and their biological activity, numerous syntheses of these derivatives have been reported employing the Smiles rearrangement, such as in the preparation of 52.^{8,28,29}

CONCLUSION

The Smiles rearrangement has been found to be an intramolecular nucleophilic aromatic substitution reaction which bases its reactivity on several well-defined factors: (1) activation of the aromatic system, (2) nucleophilic activity of the attacking group, (3) the nature of the linkage between the nucleophile and leaving group, and (4) the effect of catalysis. This type of rearrangement has often found great usefulness in the synthesis of novel heterocyclic systems.

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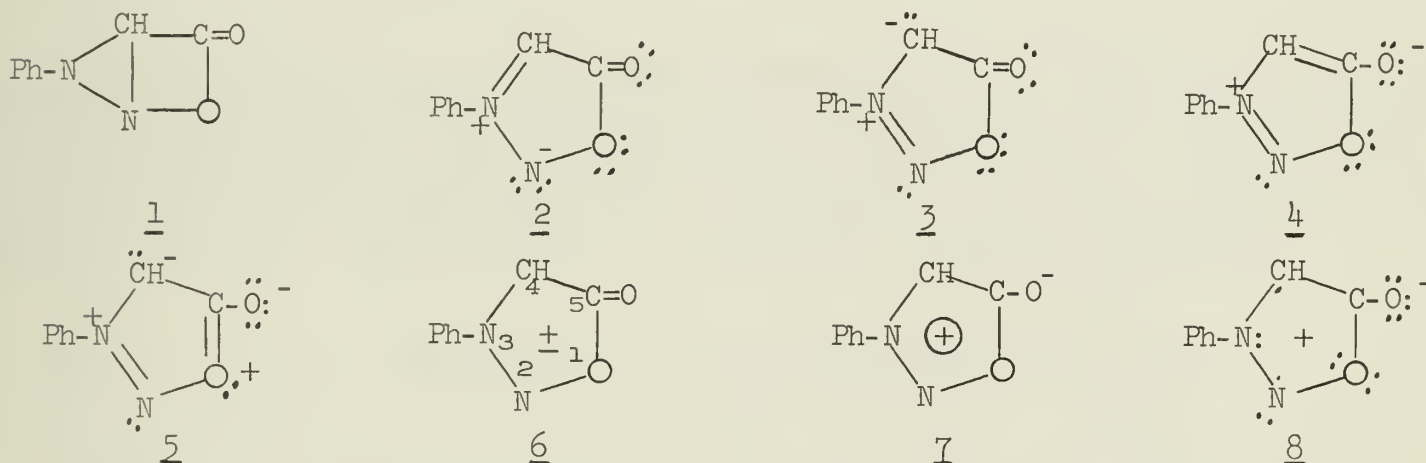
SYDNONE CHEMISTRY

Reported by Robert H. Williams

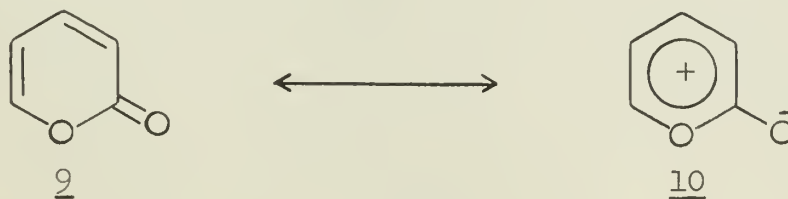
December 2, 1968

The sydnone ring has sufficient aromatic character to undergo electrophilic substitution reactions, yet it is readily hydrolyzed. Despite the aromaticity of sydnones, no significant contribution to their ground state is made by any covalent limiting resonance structure. Sydnones undergo cycloaddition-cycloelimination reactions readily, since formation of the typical transition state is accompanied by loss of the zwitterionic character of the ground state. It is the purpose of this seminar to review sydnone chemistry with an emphasis on recent work.

In 1935, Earl and Mackney¹ assigned the name N-phenylsydnone and structure 1 to a compound that was produced by the dehydration of N-nitroso-N-phenylglycine. This postulated structure, however, was not in accord with observed chemical reactions. The compound cannot be represented satisfactorily by any covalent structure, and is now considered to be a hybrid of dipolar and tetrapolar limiting resonance structures.² Structures 2 through 5 are examples of the several possible limiting resonance structures. A priori, none of these limiting resonance structures adequately represents



the resonance hybrid, and special symbolism has been employed. The symbolism of structure 6 emphasizes the zwitterionic and aromatic nature of sydnones and other mesoionic compounds. Baker and Ollis³ have suggested the use of the word mesoionic to describe heterocycles which cannot be satisfactorily represented by any covalent structure, and which possess a sextet of pi electrons in association with the atoms comprising the ring. The symbolism of structure 7 emphasizes the aromaticity of the ring due to the six pi electrons which may be thought of as having arisen from sources indicated in structure 8. Analogous symbolism has been used to indicate the pseudo-aromatic character of 2-pyrone (9,10).⁴ The use of the symbolism of structures 7 and 10 must be understood to mean only a partial charge separation, just as the symbolism of structure 6 must be understood to mean only partial double bond character of the exocyclic C-O bond. Finally, it must be mentioned that representation of the hybrid by one of the dipolar limiting resonance structures, for convenience, is also encountered.



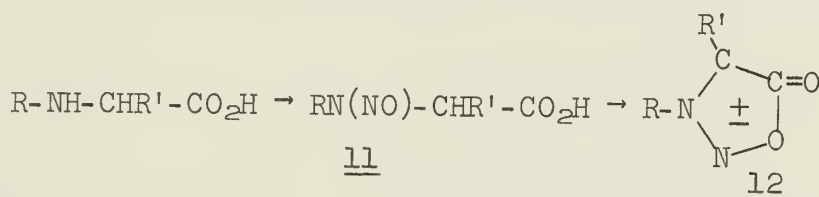
The nomenclature ψ -5-keto-3-phenyl-3,5-dihydro-1-oxa-2,3-diazole has been proposed as an alternative to the trivial name N-phenylsydnone, but the trivial nomenclature is in general use.⁵

Aromaticity of the sydnone ring is indicated by the chemical shift of the ring proton, the frequency of C-H stretch, and the frequency of maximum ultraviolet absorption. Depending upon the substituent at position 3, the chemical shift (δ) is 6.19 - 6.78 ppm⁶ and the C-H stretch appears at 3140-3190 cm⁻¹.⁴ A single peak ($\lambda_{\text{max}} \sim 290$ nm, $\epsilon \sim 8000$) is present in uv spectra of various N-alkylsydnones.⁷ As shown in Table I, bond lengths are generally in good agreement with those measured in aromatic model compounds.

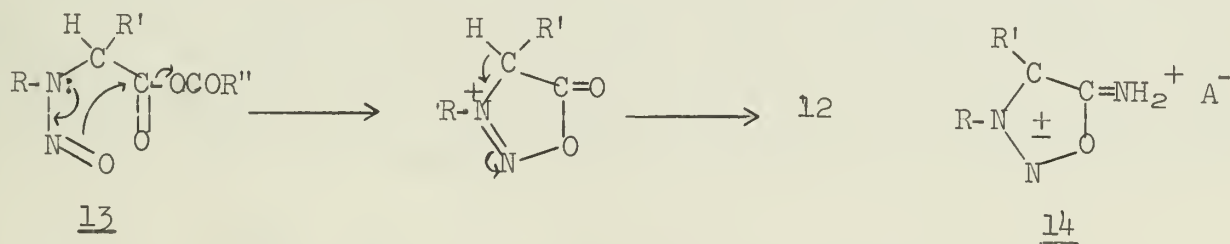
Table I.⁸ Bond Lengths of 1,2-Bis(3-(4-chlorosydnonyl))ethane and Model Aromatic Compounds (X-Ray)

Sydnone Bond	Length, Å	Model	Length, Å
Ring-O-N	1.389	1,2,5-oxadiazole	1.380
N-N	1.313	1,2,4,5-tetrazine	1.321
N-C	1.344	pyridine	1.340
C-C	1.395	benzene	1.397
C-Ring-O	1.407	4-hydroxycoumarin	1.37
C-O	1.215	4-hydroxycoumarin	1.20

N-Phenylsydnone undergoes electrophilic substitution at position 4. Halogenation,² nitration,⁵ acylation,⁵ and sulfonation⁹ have been observed. The 4-bromo compound forms a Grignard reagent, and N-phenylsydnone can be converted to a lithium salt by n-butyllithium.^{10,11} Treatment of N-phenylsydnone with hydrogen peroxide results in the formation of 3,4-diphenylsydnone. Hashimoto and Ohta¹² have postulated a free radical mechanism. N-phenylsydnone is brominated by N-bromosuccinimide.²



Sydnones are prepared by dehydration of N-Alkyl or N-aryl-N-nitroso- α -amino acids.⁵ While acetic anhydride is commonly used for the dehydration, the reaction is much faster when trifluoroacetic anhydride is employed. The formal mechanism involves the mixed anhydride 13. The mixed anhydride may be prepared from the potassium

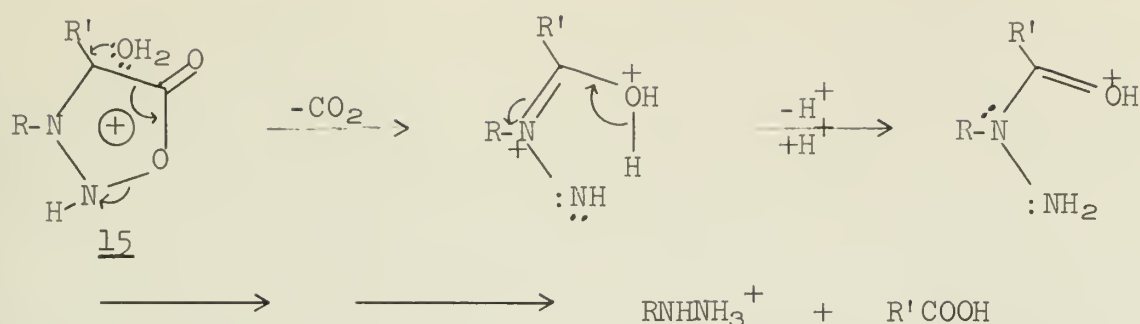


salt of 11 and acetyl chloride, and thermal decomposition produces the sydnone in high yield.⁵ Dehydration of the acid with N,N'-diisopropylcarbodiimide has also been reported.

Treatment of the nitrile corresponding to 11 with acid results in the formation of a salt of the analogous mesoionic N-alkyl or N-arylsydnonimine 14.¹³

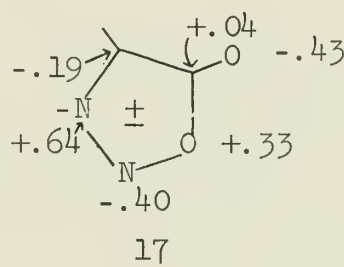
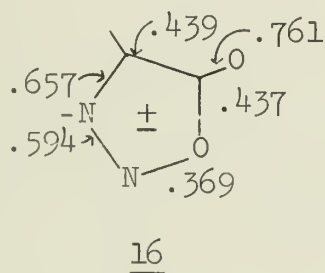
Base catalyzed hydrolysis of sydnones results in the regeneration of the N-alkyl or N-aryl-N-nitroso- α -amino acid (as the salt). The accepted mechanistic sequence¹⁴ involves nucleophilic attack at position 5, ring opening, and a tautomeric shift.

Acid catalyzed hydrolysis of sydnones has been used as a synthetic route to alkylhydrazines,¹⁵ and probably proceeds via nucleophilic attack at position 4 of a protonated sydnone (15), causing ring cleavage with the loss of carbon dioxide.¹⁴ Tracer studies indicate that no scrambling of the nitrogen atoms occurs during the reaction.¹⁶ The rate of hydrolysis of N-alkylsydnones increases with steric requirements of the substituent.¹⁴

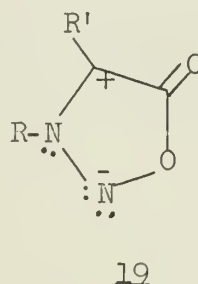
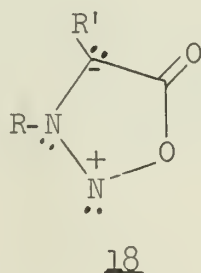


Double bond character of the exocyclic C-O bond is indicated by bond lengths (determined by X-ray studies of 1,2-bis(3-(4-chlorosydnonyl))ethane,⁸ see Table I, and N-(p-bromophenyl)sydnone⁵) and by carbonyl stretching frequency. The frequency at which carbonyl absorption is observed is strongly dependent upon the nature of the substituents and upon the solvent.

The zwitterionic nature of sydnones is indicated by their high dipole moments. The dipole moment of N-phenylsydnone is 6.57 D.¹⁷ Partial positive charge at position 3 is demonstrated by the deactivation to electrophilic attack of the benzene ring in N-phenylsydnone. Partial negative charge at position 4 is demonstrated by the activation to electrophilic attack of the benzene ring in N-methyl-C-phenylsydnone (12; R = Me, R' = Ph).⁵ The pi bond orders shown in 16 and the charge distribution shown in 17 resulted from molecular orbital calculations for the sydnone ring by the method of Pariser-Parr-Pople-Brown and Heffernan,¹⁸ and are in agreement with experimental observations.



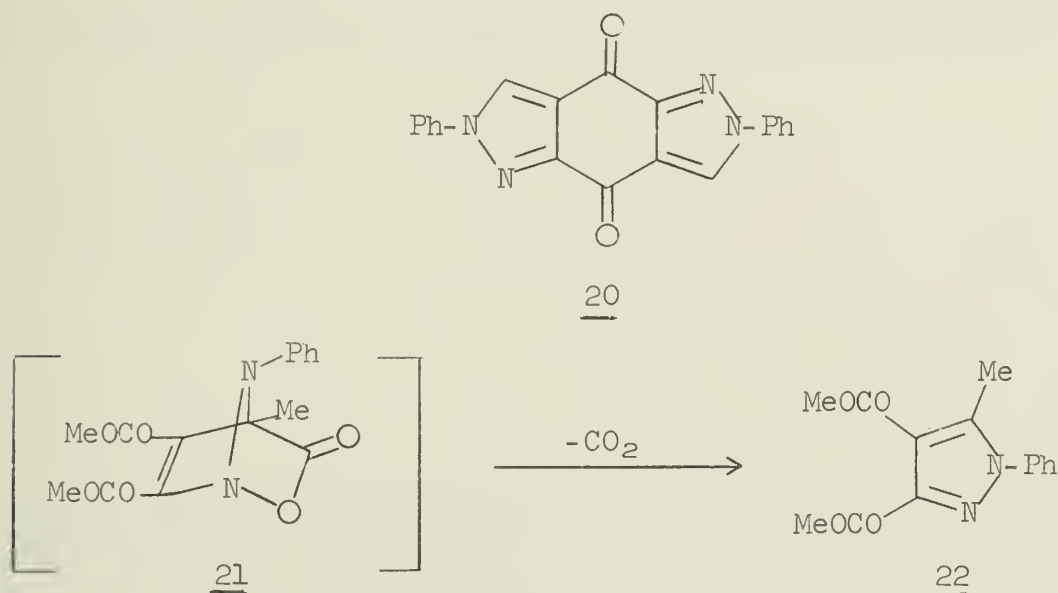
In addition to limiting resonance structures of types already presented, "sextet" structures¹⁹ 18 and 19 should be mentioned. These structures emphasize the 1,3-dipolar nature of sydnone. The positive character of position 3 of the sydnone ring is an indication that neither of these can be major contributor to the ground state. Nevertheless, contributions from structures of this type increase the polarizability of the hybrid, and are of importance when considering intermolecular interactions.



As predicted by inductive effect considerations, the chemical shift (acetone-d₆, extrapolated to infinitely dilute solution) of the ring proton of various N-alkylsydnones decreases in the order Me > Et > i-Pr > t-Bu. This order is reversed when the spectra are run in chloroform-d. Lawson, Brey, and Kier²⁰ have rationalized

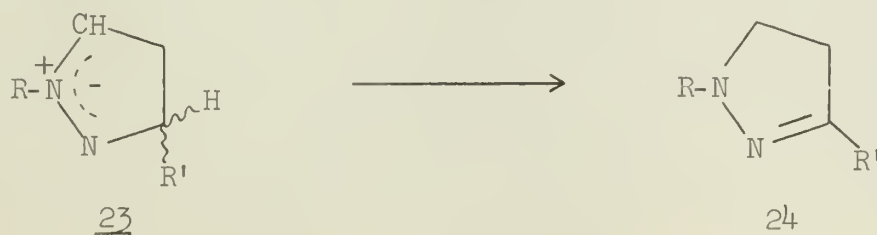
this behavior in terms of stabilities of aggregated states of sydnones. Presumably, only the more highly aggregated states are encountered in acetone solution, but in dilute chloroform solution, hydrogen bonding can help destabilize the more highly aggregated states. Substituent effects would be due to decreasing stability of the more highly aggregated states with increasing size of the alkyl substituent. The chemical shift of the ring proton increases with the extent of solvation of solute.

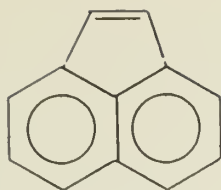
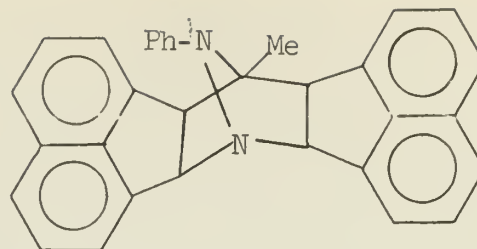
Hammick and Voaden²¹ assigned structure 20 to a product that they obtained by the treatment of N-phenylsydnone with p-benzoquinone. This appears to be the first reported instance of a general reaction of sydnones: a cycloaddition-cycloelimination reaction. Huisgen and his coworkers²² obtained dimethyl 1-phenyl-5-methylpyrazole-3,4-dicarboxylate (22) in 99% yield by treating N-phenyl-C-methylsydnone with dimethyl acetylenedicarboxylate in boiling xylene. The reaction proceeds via loss of carbon dioxide from the adduct (21) arising from cycloaddition of N-phenyl-C-methylsydnone to the dipolarophile. That the reaction does proceed through adduct 21 is shown by the observation²³ that sydnones are stable at 200° in the absence of dipolarophiles. The rate of reaction is controlled by the rate of formation of adduct.²⁴ Decarboxylation of the adduct occurs at such a high rate that no measurable concentration of adduct has ever been detected.



The use of alkenes as dipolarophiles leads, after loss of carbon dioxide from the initially formed adduct, to a new 1,3-dipolar compound (23) which can tautomerize to a non-zwitterionic Δ^2 -pyrazoline, 24.²⁵ Evidence for the 1,3-dipolar intermediate is obtained by a study of the products of reaction of N-phenyl-C-methylsydnone with acenaphthylene, 25.²³ In addition to the expected Δ^2 -pyrazoline, product 26 is formed. This product arises by the addition of a second molecule of acenaphthylene to the dipolar intermediate.

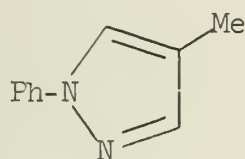
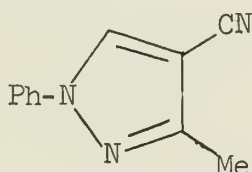
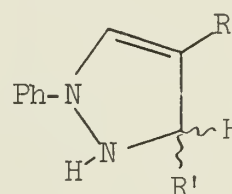
Upon treatment with sydnones, α,β -unsaturated nitriles or carboxylic acid esters form pyrazoles. Thus, N-phenylsydnone reacts with acrylonitrile to form 1-phenylpyrazole. Vasil'eva, Yashunskii, and Shchukina²⁶ postulated that the reaction proceeded through an intermediate Δ^2 -pyrazoline.



2526

The products of the reaction of N-phenylsydnone and crotononitrile are 1-phenyl-4-methylpyrazole (27) and 1-phenyl-3-methyl-4-cyanopyrazole (28). This cannot be interpreted in terms of a Δ^2 -pyrazoline, but loss of HCN from Δ^4 -pyrazoline 29 (R = Me, R' = CN) would produce 27, and loss of hydrogen from the isomeric Δ^4 -pyrazoline (29; R = CN, R' = Me) would produce 28.²⁷

Also in support of the Δ^4 -pyrazoline intermediate, and considerably more startling, is the reaction of N-phenylsydnone and 2-phenylpropene to produce carbon dioxide, methane, and 1,3-diphenylpyrazole.²⁸ Reaction with 1,1-diphenylethylene produces 1,3-diphenylpyrazole (67% yield) via loss of benzene from the intermediate. The reaction of 1,1-diphenylethylene with N-phenyl-C-methylsydnone produces the corresponding pyrazole in 99% yield.

272829

The mechanism initially proposed for adduct formation proceeds through a zwitterionic intermediate formed by attack of position 4 of the sydnone ring by the "electrophilic carbon atom" of the dipolarophile.²⁹ The ability of polar solvents to help stabilize zwitterionic species would form the basis for a proportionality between rate of reaction and dielectric constant of the solvent.¹⁷ The rate of reaction is observed to decrease slightly with increasing dielectric constant of the solvent, thus the rate-determining formation of adduct does not involve a zwitterionic intermediate.

The rate of reaction is greatly enhanced by the choice of a dipolarophile in which a carboalkoxy or phenyl substituent is conjugated with the multiple bond. Firestone³⁰ has proposed a two step addition involving an intermediate spin-paired diradical. Were this the mechanism of the reaction, the observed substituent effect could be explained in terms of stabilization of the diradical intermediate produced in the rate determining step of adduct formation.

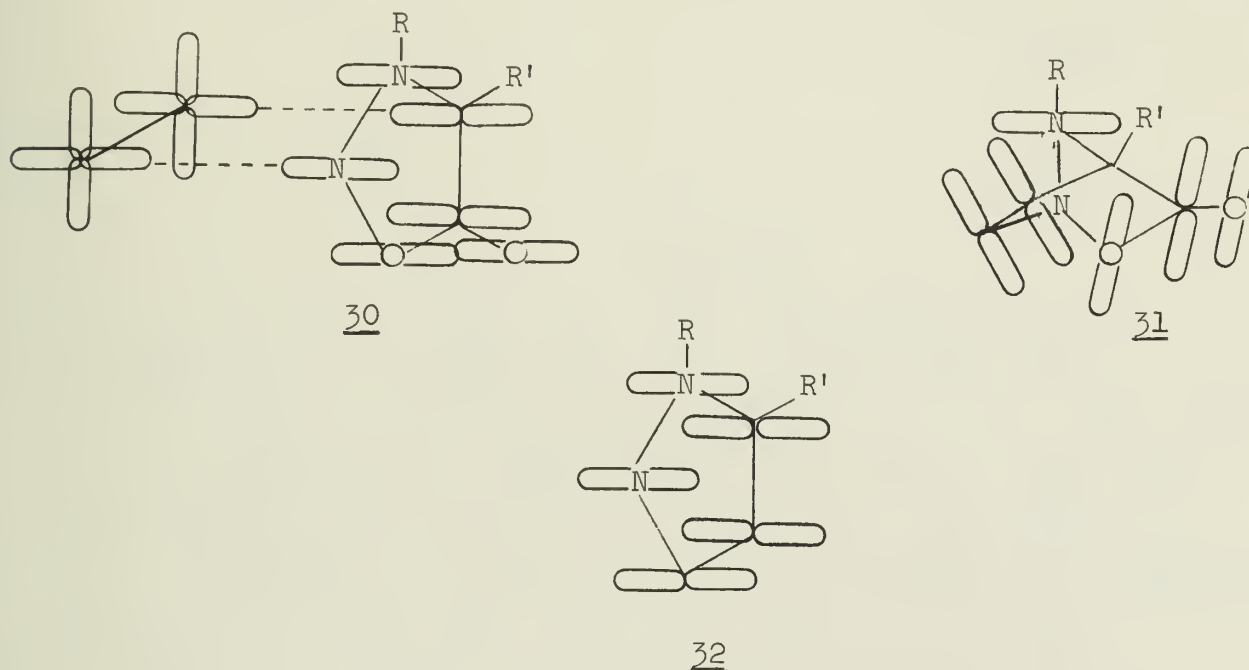
The reaction has a large negative entropy of activation.²⁴ Presumably, the step that would involve a large negative entropy of activation would not be the formation of the diradical, but the closing of the diradical to form the cycloadduct.

The product obtained from the reaction of 1,3-dipole with 2-phenyl-1,3-butadiene permits decision between concerted cycloaddition and two-step diradical mechanism. If the diradical mechanism prevails, the 1,2 bond should be preferred, due to stabilization of the diradical by the phenyl group. The concerted process, on the other hand, favors reaction at the less highly substituted 3,4 bond. The only product obtained from the reaction of 2-phenyl-1,3-butadiene with a related 1,3-dipole results from addition to the 3,4 double bond.³¹ The reaction of 2-phenyl-1,3-butadiene with sydnone has not been reported.

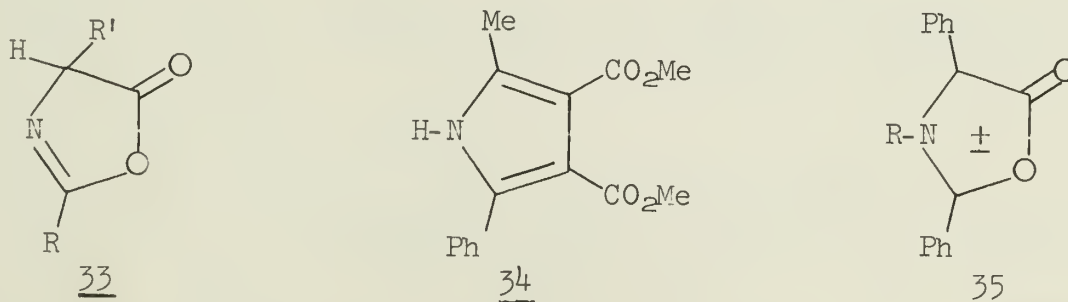
A concerted process would be in accord with the observed small dependence of rate on solvent. Also, such a process would be expected to have a large negative

entropy of activation. The substituent effect has been attributed to the increase in polarizability of the pi bond that accompanies conjugation.¹⁷ Finally, the cycloaddition of dipolarophile to the sydnone and the cycloelimination of carbon dioxide from the adduct are thermally allowed electrocyclic processes.³¹⁻³⁴

The formation of pyrazoles from sydnones and acetylenes proceeds through orientation complex 30 to the bicyclo adduct 31 and on to the pyrazole 32. The substituents on the molecule of dipolarophile have been omitted, as have the non-bonding pi orbitals of the oxygen atoms and the nitrogen atom in position 2 of the sydnone ring. Rehybridization accompanies interaction of the two pi systems.



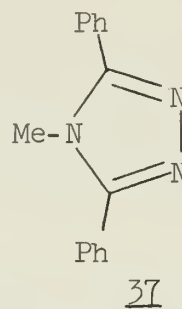
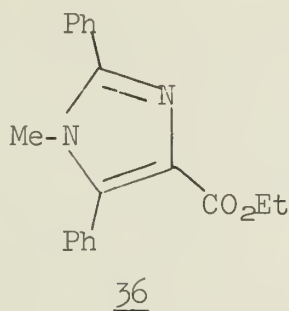
Cycloaddition-cycloelimination reactions of this type are not limited to sydnones, nor are they limited to dipolarophiles of the type C=C and C≡C. Dehydration of an N-acyl- α -amino acid with acetic anhydride gives rise to an azlactone (33). The azlactone obtained from N-benzoylalanine (33; R = Ph, R' = Me) and the isomeric azlactone obtained from N-acetylphenylglycine (33; R = Me, R' = Ph) both react with dimethyl acetylenedicarboxylate at elevated temperatures to produce the same substituted pyrazole (34). Huisgen¹⁹ has postulated a mechanism which proceeds via cycloaddition of dipolarophile to, and cycloelimination of carbon dioxide from a mesoionic tautomer of the azlactone.



Dehydration of N-benzoyl-N-methylphenylglycine with acetic anhydride results in the formation of anhydro-5-hydroxy-3-methyl-2,4-diphenyloxazolinium hydroxide (35; R = Me), a mesoionic compound which Huisgen prefers to refer to as münchnone. Münchnone is much more reactive than any sydnone: hydrolysis takes place upon exposure to atmospheric moisture, and cycloaddition-cycloelimination proceeds at 0° with methyl propiolate. The sulfur analog of münchnone is formed when a solution of münchnone in cold carbon disulfide is allowed to stand.

Münchnone undergoes the cycloaddition-cycloelimination reaction with ethyl cyanoformate to produce the substituted imidazole 36. The reaction of münchnone

with diethyl azodicarboxylate at 0° produces 4-methyl-3,5-diphenyl-1,2,4-triazole (37) and tetraethyl hydrazinetetracarboxylate. Huisgen¹⁹ has proposed a reaction sequence involving transfer of two carboethoxy groups from the 1,3-dipole which arises from cycloaddition-cycloelimination to a molecule of diethyl azodicarboxylate.



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RECENT STUDIES CONCERNING HOFMANN AND RELATED BIMOLECULAR ELIMINATIONS

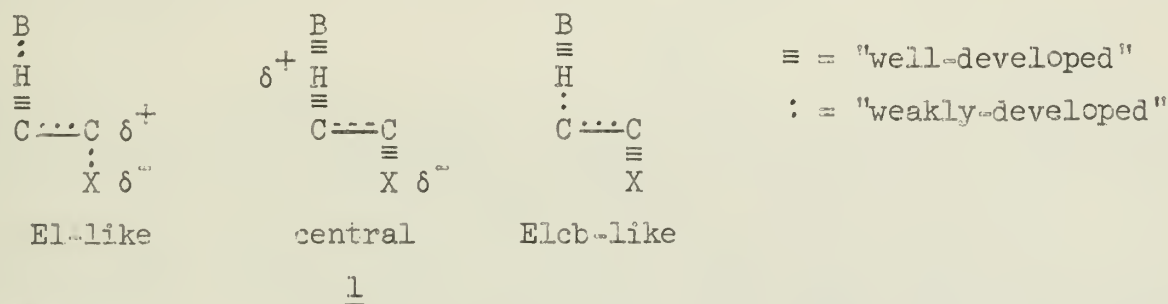
Reported by Richard E. L. Henderson

December 5, 1968

INTRODUCTION

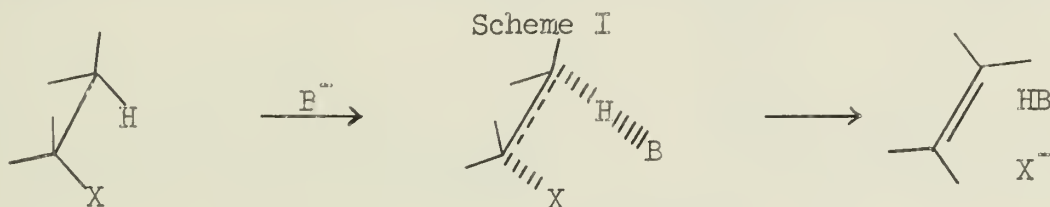
Hofmann eliminations of trimethylammonium compounds to form olefins have traditionally been considered to proceed by an exclusively anti elimination mechanism. The base-induced eliminations of other 'onium compounds, as well as of halides, tosylates, and the like, have been considered to proceed similarly.¹ In recent years, however, evidence has been presented by numerous workers which challenges the mechanistic view that syn-eliminations are confined to reactions such as the pyrolysis of amine oxides, the Chugaev (xanthate pyrolysis) reaction, and the pyrolysis of acetate esters.

The anti elimination of 'onium compounds may be envisioned as passing through transition states ranging from E1 (carbonium) through E2 (concerted) to Elcb (conjugate-base carbanion). Indeed, the E2 mechanism is often described as ranging from "E1-like" to "Elcb-like" (1).² Although reference has been made to compounds



with stabilizing substituents undergoing E1 eliminations,³ such compounds are rare in 'onium eliminations.

Currently, several research groups are investigating the possibility of a syn E2 elimination mechanism by which the leaving group and the proton to be removed by base are approximately coplanar and stereochemically cis to each other (Scheme I).



Coke⁴ has suggested that the choice of model compounds in early studies of Hofmann eliminations was the basis of the conclusion that only the anti elimination mechanism occurs. In order to eliminate the possibility of two or more removable protons, the β -carbon was di-substituted and the α -carbon was substituted in addition to the leaving group so that only one reactive proton was available for elimination and so that product analysis would be unambiguous. As a result, large steric interactions between the substituents on the adjacent carbon atoms effectively prohibited the eclipsed form needed for any syn elimination. Comparative rate studies and labeling experiments were therefore needed for determination of the mechanism of elimination.

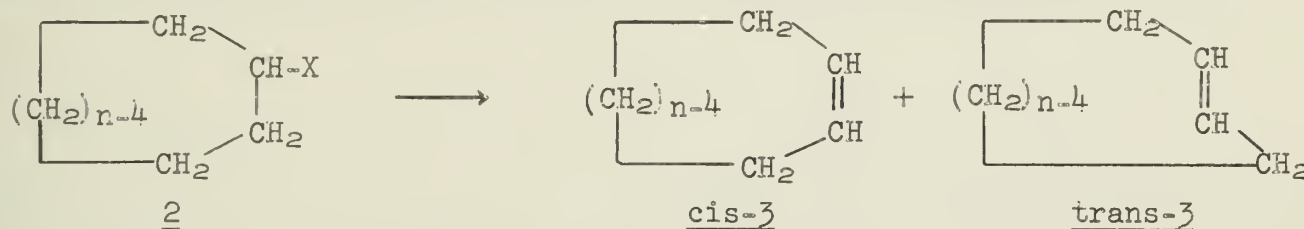
THEORETICAL GROUNDS FOR SYN ELIMINATION

Using the principle of least motion suggested by DePuy and others,⁵ Hine⁶ set about determining the likely dihedral angles for reaction of ethyl chloride to give ethylene. According to the principle of least motion, those elementary reactions will be favored which involve the least change in atomic position and electronic configuration. Least squares distances (the sum of the squares of the distances through which the six "unreacting" atoms of ethyl chloride must move during the elimination) were calculated for initial dihedral angles of 0° , 60° , 120° , and 180° . As expected, the smallest least squares distance, 0.185 Å, was for 180° , the initial angle for anti elimination. For 60° and 120° the distances were much larger, 1.326 and 1.130 Å, respectively, again essentially as expected. For 0° , corresponding to

pure syn elimination, the least squares distance was only 0.421 Å. Consequently, although anti elimination would be predicted to be faster than syn elimination, it would not be illogical to suggest the possibility of a syn E2 elimination. By extension, other elimination reactions might be expected to proceed in part by a syn elimination.

EVIDENCE FOR A SYN MECHANISM BY RATE PROFILE ANALYSIS

Sicher and his coworkers have carried out extensive studies of the stereochemistry of elimination reactions involving cyclic aliphatic compounds. In some of their earlier studies,^{7,8} they reported the rates of reaction for a homologous series of cycloalkyldimethylamine oxides (2, X = N(CH₃)₂O) in t-butyl alcohol and for a homologous series of cycloalkyltrimethylammonium chlorides (2, X = N(CH₃)₃) with potassium t-butoxide in t-butyl alcohol. Taking note of the fact that the elimination



of amine oxides is generally accepted as proceeding by a predominantly syn mechanism, the authors prepared rate data plots relating ring sizes of the cis- and trans-olefin products to first order rate constants for the tertiary-amine oxides and to second order rate constants for the quaternary-ammonium chlorides (Figure 1). The striking similarity in the shapes of the plots for the trans-cycloolefins led to the hypothesis that the quaternary-ammonium salt elimination forms trans-cycloolefins predominantly by a syn mechanism. Cis-cycloolefins, on the other hand, apparently result from a "normal", predominantly anti, mechanism.

Further investigation into ring-size effects for cycloalkyl bromides (2, X = Br)⁹ led to the discovery that the solvent used for the eliminations could have a drastic effect on the rates of formation of the trans-olefins relative to those of

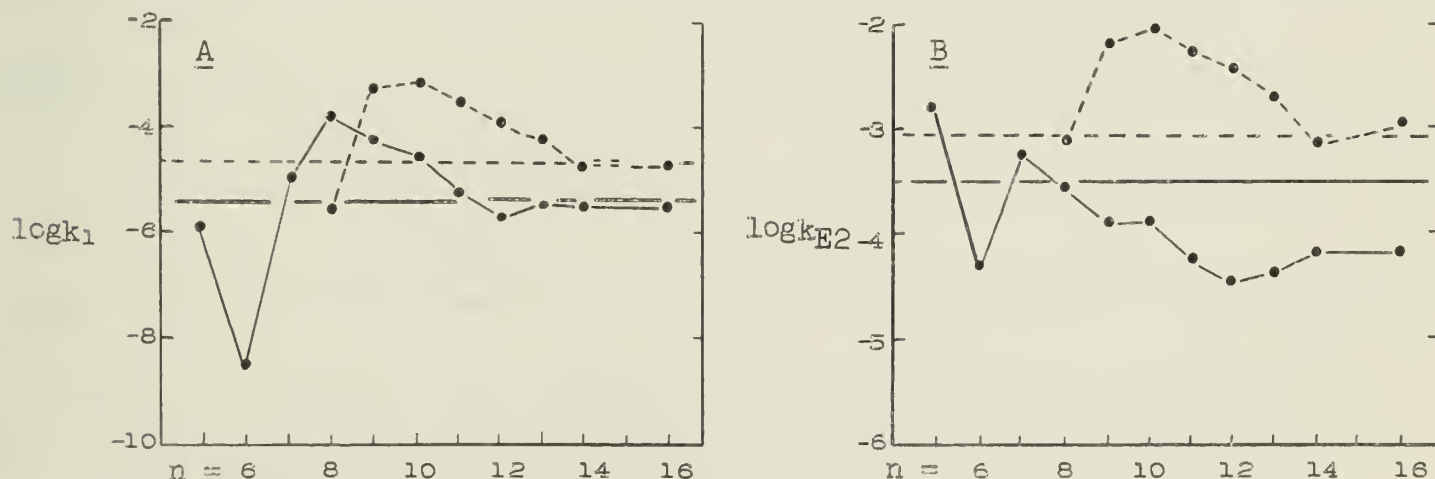
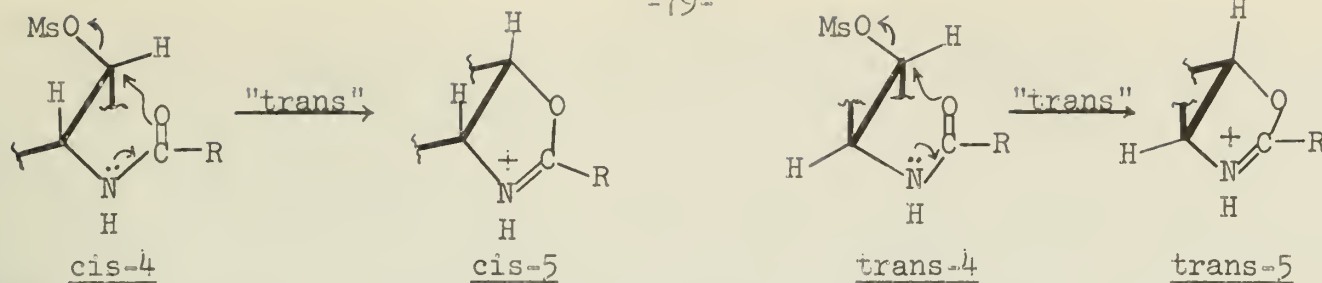


Figure 1. Formation rate constants for (A) E1 eliminations of cycloalkyldimethylamine oxides in t-BuOH at 70.6°C and (B) bimolecular eliminations of cycloalkyltrimethylammonium chlorides (0.03M) with t-BuOK (0.11M) in t-BuOH at 55°C. Solid lines refer to formation of cis-olefins; dashed lines, to trans-olefins. Horizontal lines refer to 4-nonenes, used as reference products.

the cis-olefins. Since anti elimination of the bromides could conceivably lead to both cis- and trans-cycloolefins, a rate study involving the intramolecular reactions of cis-4 and trans-4 to cis- and trans-Δ²-oxazolines (5) was used in conjunction with the earlier amine oxide studies to determine qualitatively the relative degrees of syn and anti eliminations for the bromides. Using linear free energy plots to compare the reference reactions with the bromide eliminations, the authors deduced that trans-cycloolefins were formed by a predominantly syn mechanism and cis-cycloolefins by a predominantly anti mechanism when t-butanol was used as solvent. In ethanol, however,



trans-cycloolefins appeared to be formed by an anti mechanism.

In more extensive studies,^{10,11} Sicher and coworkers investigated the effects of solvent and base changes. In preliminary investigations¹⁰ rate profiles were constructed for eliminations of cycloalkyl bromides using t-BuOK in t-butanol and in benzene, EtOK in ethanol, and t-BuOLi in dimethylformamide (Figure 2, A-D).

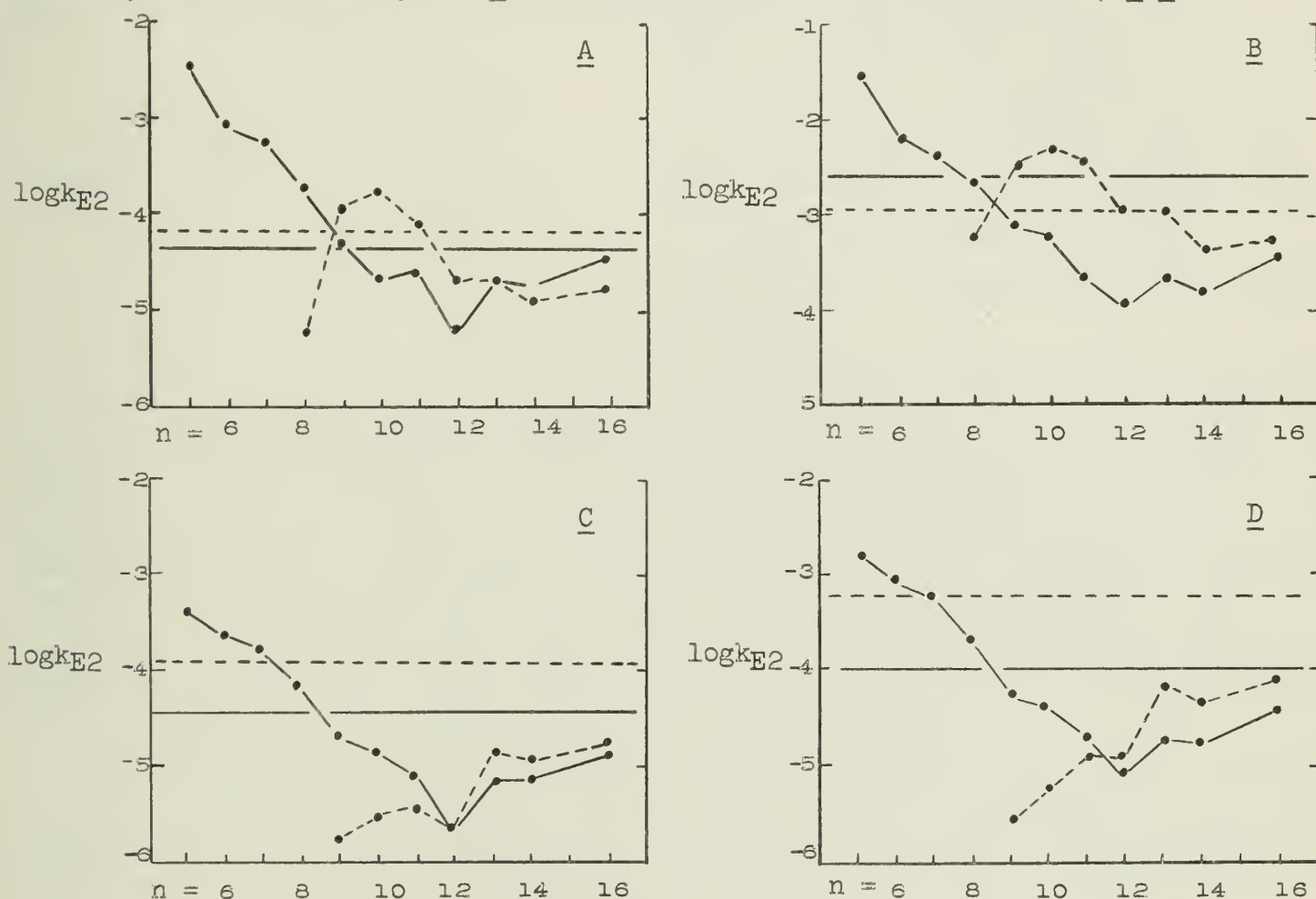


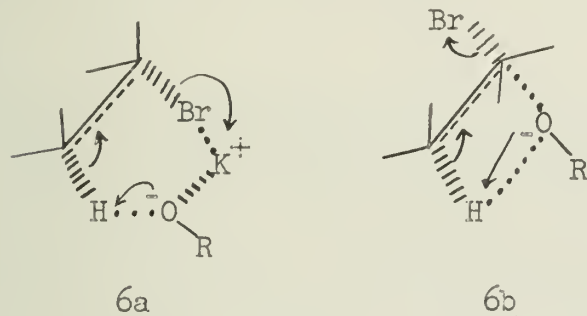
Figure 2. Formation rate constants vs. ring size for the bimolecular eliminations of cycloalkyl bromides using (A) t-BuOK in t-butanol at 82.5°C, (B) t-BuOK in benzene at 100°C, (C) EtOK in ethanol at 58.5°C, and (D) t-BuOLi in DMF at 40°C. Solid lines refer to formation of cis-olefins; dashed lines, to trans-olefins. Horizontal lines refer to 4-nonenenes from 5-nonyl bromide, used as references.

Comparison of the data with that in Figure 1 led to the conclusion that the weakly dissociating solvents t-butanol and benzene tended to favor syn elimination to trans-cycloolefins and anti elimination to cis-cycloolefins. The more strongly dissociating solvents ethanol and DMF, however, tended to favor the anti mechanism for both cis and trans-cycloolefins. For the cycloalkyl bromides, then, as for the quaternary-ammonium compounds, the authors supported syn eliminations analogous to the amine oxide pyrolyses and anti eliminations analogous to the syntheses of Δ^2 -oxazolines.

The somewhat more detailed investigations¹¹ involved more base-solvent systems than had the preliminary work. Each of three bases - t-BuOK, CH₃OK, and C₆H₅OK - was used in conjunction with four solvents - benzene, DMSO, t-butanol, and methanol - to induce eliminations of cycloalkyltrimethylammonium chlorides. With minor exceptions for the methanol systems, the change from strong base (t-BuOK) to weak base (C₆H₅OK)

resulted in very large decreases in the % trans-olefin/% cis-olefin ratios for all the ring systems (eight to fourteen membered) studied. Furthermore, for the aprotic solvents benzene and DMSO, trans products were favored in the less polar solvent (benzene). Similarly, for the protic solvents t-butanol and ethanol, trans products were favored in t-butanol.

The conclusions drawn from the studies involving base-solvent dependence were that the syn mechanism was favored in eliminations taking place in poorly- or non-dissociating solvents and that greater basicity induced increased syn elimination. Sicher *et al* suggested that the non-dissociating solvents permit the formation of base-counter ion pairs which may help stabilize the nearly-eclipsed transition state (6a) by assisting in the removal of the leaving group. Strongly-ionizing solvents, on the other hand, would prevent high concentrations of such ion pairs, so that the anti transition state (6b) would be stabilized in part by the anionic moiety of the base. The S_N2 displacement of cycloalkyldimethylamine from ammonium chlorides¹² was



found to compete with elimination; moreover, factors which favored elimination favored syn elimination. In addition the nonyl reference compounds^{10,11} and other open-chain compounds studied¹³ indicated that the syn and anti eliminations operated for open-chain compounds to some extent.

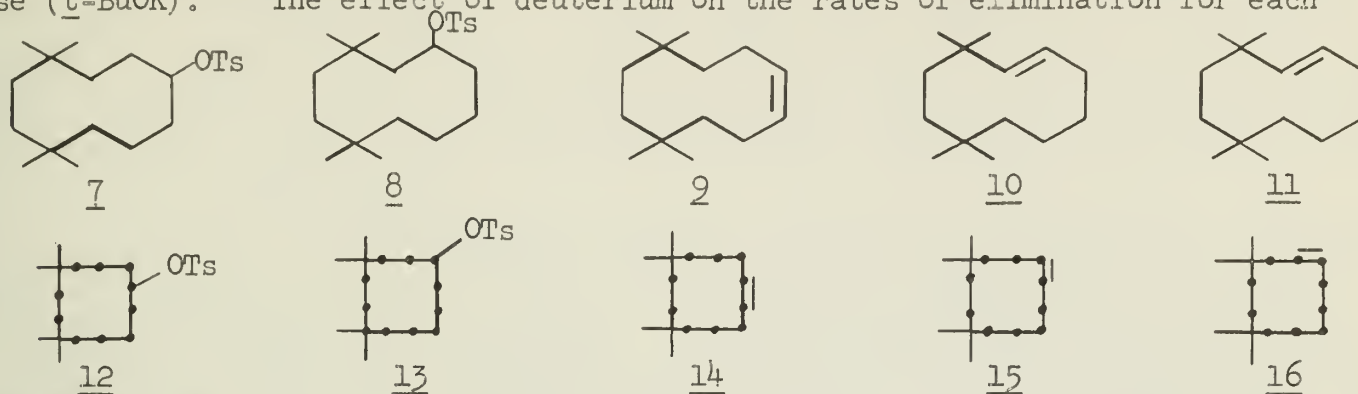
EVIDENCE FOR A SYN MECHANISM FROM LABELING STUDIES

Further elucidation of the mechanism of elimination required the use of deuterium labeling, performed in such a way as to place deuterium atoms on the carbon atoms bearing the leaving group or on those adjacent. The use of $LiAlD_4$ and B_2D_6 with ketones, epoxides, and olefins provided the main steps for synthesis of labeled alcohols,¹⁴ which could be converted to tosylates with retention of configuration with tosyl chloride and then to quaternary-ammonium salts with trimethylamine with inversion. Primary cis- β -D amines could be synthesized more directly using B_2D_6 and NH_2Cl and then could be converted to the quaternary salts.⁴ The ammonium hydroxides used in Hofmann eliminations were prepared from the salts using either moist Ag_2O or, preferably, an anion exchange resin. Kinetic hydrogen isotope effects were either calculated or estimated in order to determine the extent of syn elimination observed.

Although most workers determined kinetic isotope effects (the ratios of rate constants for undeuterated species to those of deuterated species) by indirect means involving product analyses, data determined directly are available for cyclohexyl tosylates.¹⁴ Aliquots taken during the course of alkoxide-induced eliminations were quenched with acid, the excess being back-titrated to obtain rate data for eliminations in ethanol (with $EtONa$) and in t-butyl alcohol (with t- $BuOK$). For cyclohexyl-1-d tosylate, the secondary isotope effect (for C_α) was found to be relatively small: k_H/k_D ($EtOH$) = 1.14 and k_H/k_D (t- $BuOH$) = 1.15. For cyclohexyl-2,2,6,6- d_4 tosylate, for which the difference in syn and anti mechanisms cannot be determined from labeling data, k_H/k_D ($EtOH$) = 4.19 and k_H/k_D (t- $BuOH$) = 6.27; although not "purely" primary, the isotope effects were sizable for the d_4 compound in both solvents. On the assumption that the undeuterated branch in cis- and trans-cyclohexyl-2-d tosylates did not show isotope effects due to labeling in the other branch, k_H/k_D was calculated for each. The calculated isotope effects for the trans-deuterated tosylate was rather large in each solvent: k_H/k_D ($EtOH$) = 4.47 and k_H/k_D (t- $BuOH$) = 7.53, as would be expected for a predominantly anti elimination. For the cis-deuterated isomer the effect was considerably smaller, with k_H/k_D ($EtOH$) = 1.36 and k_H/k_D (t- $BuOH$) = 1.51, indicating to the authors that a secondary isotope effect at the β -carbon was affecting the rate of anti elimination. The possibility of a true secondary effect being much less significant, with a noticeable primary effect due to a slow syn elimination (See Figures 1 and 2 for cyclohexyl compounds, $n = 6$), was not suggested by the authors, but the data are not inconsistent with such an explanation.

Various monodeuterated 1,1,4,4-tetramethylcyclodecyl-7-tosylates (7) and 6-

tosylates (8) were synthesized by Sicher and workers for use in solvolytically-induced elimination reactions in acetic acid, DMF, pyridine, DMSO, and collidine.¹⁵ The tosylates 7 and 8, along with 1,1,4,4-tetramethylcyclododecyl-8-tosylates (12) and 7-tosylates (13), were used in labeling studies involving eliminations via strong base ($t\text{-BuOK}$).¹⁶ The effect of deuterium on the rates of elimination for each

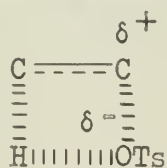


deuterated compound was determined; product ratios were then used to determine the extent of syn and anti elimination for each compound. Since product yields were obtained by vapor phase chromatography, the extent of deuterium labeling in each olefin could not be determined directly. Isotope effects, therefore, were estimated by comparisons between product yields of the olefins produced from the unlabeled and labeled precursors. Although the authors realized that the exact extent of pathway selectivity could not be obtained from comparative rate studies and from analyses of mixed products,¹² they concluded that the data available from the labeling studies^{15,16} should indicate any predominating pathway leading to particular products.

Data for the elimination of 1,1,4,4-tetramethylcyclododecyl-7-D-7-tosylate, which retained the label for any β -elimination pathway, by solvolysis or using potassium t -butoxide, gave unambiguous information. Virtually no difference in product ratios for the 7-D-7-tosylate and for the 7-tosylate was observed, indicating the absence of any significant secondary isotope effect at the α -carbon.

Primary isotope effects, involving potentially removable deuterium ions, were determined for both the trans-olefin formations and the cis-olefin formations. The isotope effect, k_H/k_D , for trans-olefin formation was calculated by determining the ratio of trans product formed by elimination of a proton from the unlabeled branch of a labeled precursor to trans product formed by elimination of a proton or deuteron from the labeled branch; the ratio determined for the labeled compound, divided by the corresponding ratio for the unlabeled cyclodecyl tosylate, was defined as k_H/k_D . An isotope effect for cis-cycloolefin formation was found similarly.

Provided that the assumptions made in the calculation of k_H/k_D were essentially correct, the solvolytically-induced eliminations¹⁵ of cis- β -D-tosylates to trans-olefins and of trans- β -D-tosylates to cis-olefins were found to be by a predominantly syn mechanism, since the isotope effects in solvolysis, k_H^1/k_D^1 , were approximately unity. For the cis- and trans- β -D-tosylates, the isotope effects were not extremely large ($k_H^1/k_D^1 \approx 1.6$), indicating that anti elimination, although observed, may have been less significant than the syn mechanism. The authors postulated a transition state (17) involving intramolecular syn elimination and which may be used to explain the small quantity of transannular elimination product observed for cyclodecyl (but not the tetramethyl cyclodecyl) tosylate.



17

For the tosylate eliminations in strong base,¹⁶ the values of k_H/k_D supported the same general mechanistic viewpoint deduced from the comparative rate studies. That is, $k_H/k_D \approx 1$ for all eliminations involving cis- β -D-tosylates and $k_H/k_D \approx 1.8 - 4.0$ for all those involving trans- β -D-tosylates. These values suggest that a single proton on each β -carbon was abstracted in both syn and anti pathways. Furthermore, the

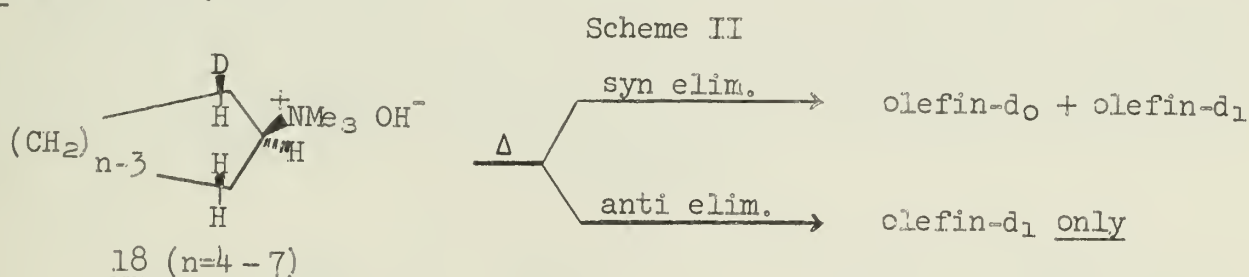
trans-olefin/cis-olefin ratio was greater for the cyclodecyl than for the cyclododecyl tosylates, suggesting decreased syn participation for the larger ring system.

Solvent changes produced altered relative yields of products and differing observed isotope effects. As the solvent was changed from DMF to t -butanol to benzene, product ratios trans-9:cis-9:trans-10:cis-10 changed from 47:37:4:12 to

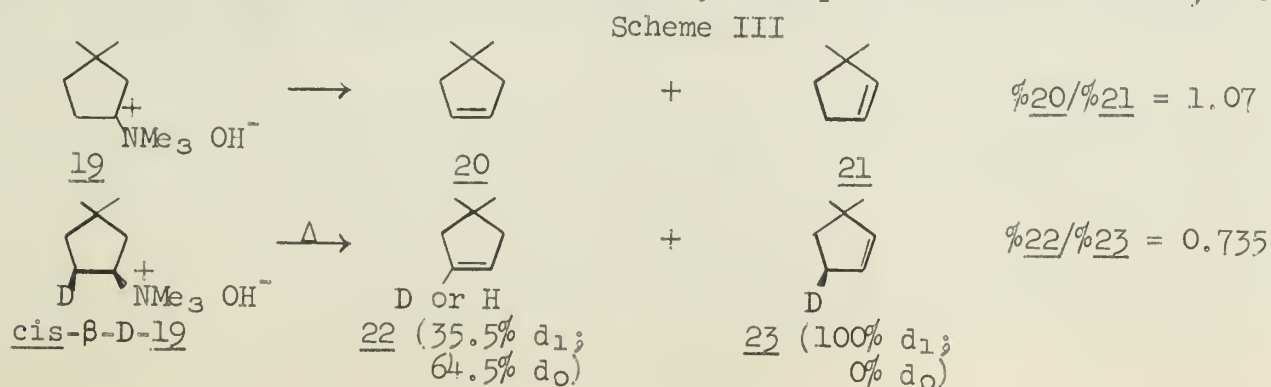
75:7:10:8 to 84:2:12:2. Corresponding values of k_H/k_D for cis- β -D-tosylates and for trans- β -D-tosylates, respectively, changed from about 1.0 and 2.3 - 4.0 to about 1.0 and 1.9 to about 1.0 and 1.9. Despite the changes in product yields, the isotope effects indicated that, at least to some extent, syn elimination produced trans-cyclodecenes and anti elimination produced cis-cyclodecenes for each solvent used. A comparison of the data for the tosylates with that estimated for cyclodecyl bromide¹¹ indicated a smaller solvent dependence for the tosylates; in benzene and *t*-butanol similar mechanistic behavior was observed for both systems, but cyclodecyl tosylate in DMF apparently underwent syn elimination to a much larger degree than did cyclodecyl bromide in the same solvent.

Studies of 1,1,4,4-tetramethylcyclodecyl tosylates¹⁶ gave somewhat different results from those of the cyclodecyl system. Products were analyzed for deuterium by mass spectrometry, and did not always show labeling as expected for an all-syn elimination to trans-olefin mechanism. In benzene syn elimination was estimated to be about 95% responsible for trans-14; in *t*-butanol, about 85% responsible; and in DMF, only about 30% responsible. Sicher and his coworkers, after obtaining roughly the same proportion of trans-cyclodecene from eliminations using unsubstituted cyclodecyl tosylate for benzene and DMF solutions as reported for the tetramethyl cyclodecenes, made the rather broad assumption that their results for the eliminations could be generalized, being approximately correct for a large variety of related eliminations.

In order to avoid possible effects caused by alkyl ring substituents, Coke and his coworkers performed the bulk of their Hofmann elimination studies on four- to eight-membered alicyclic amines bearing no ring substituents other than deuterium labels and the amine function.^{4,17,18} Products were separated by vapor phase chromatography and then analyzed by mass spectrometry in order to determine labeling, and, therefore, the role of each elimination pathway, more exactly than in earlier labeling studies.^{14,15,16} All syntheses were performed to give cis deuteration, and all the quaternary-ammonium compounds formed were compared with authentic samples or were found to have the correct physical constants. Deuterium content for both reactants and products were determined by mass spectrometry. Degradation of the ammonium hydroxides was either by normal methods under slight vacuum at 100°C ("wet conditions") or by drying at 10⁻⁷ mm Hg with decomposition directly into the mass spectrometer ("dry conditions"). Scheme II indicates the expected routes for elimination by syn and anti mechanisms.



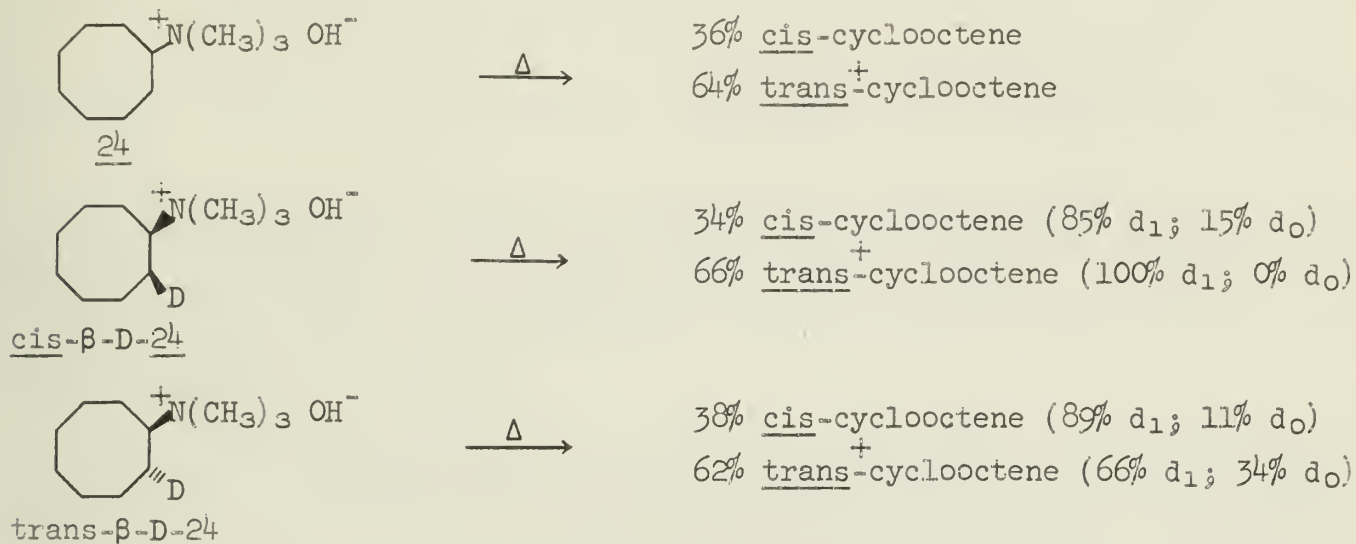
Since the products formed contained no ring substituents other than possible deuterium labels, isotope effects were determined for other systems which might approximate the behavior of the cycloalkyl ammonium hydroxides. The 3,3-dimethylcyclopentyl system, despite the substitution, was used to calculate an isotope effect for the syn mechanism since the transition state would not be expected to show torsional strain. Scheme III shows the reaction scheme and results obtained by VPC and mass spectrometry. Assuming that any secondary isotope effects were minor, the authors



calculated an isotope effect for the syn elimination: $\text{syn } k_H/k_D = 1.71$.

The smallest ring system capable of forming both cis- and trans-cycloolefins, the cyclooctyl system, required a different approach to calculating the isotope effect.^{4,17} Scheme IV indicates the products and analyses for cyclooctyl-N,N,N-trimethylammonium hydroxide. Since cis- β -D-24 yielded trans-cyclooctene with 100%

Scheme IV

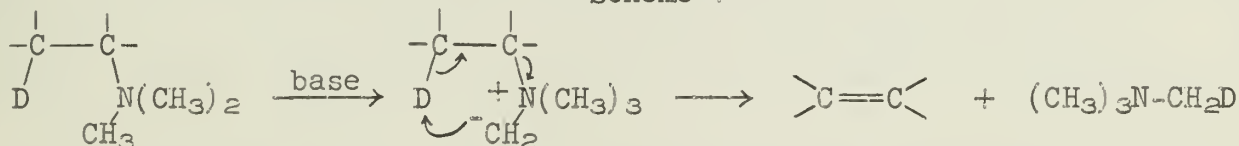


retention of deuterium, the syn mechanism was apparently responsible for the formation of all the trans product. The ratio of trans-cyclooctene-d₁ to trans-cyclooctene-d₀ calculated from the elimination of trans- β -D-24, therefore, was taken as the syn isotope effect, or $k_H/k_D = 1.94$. The possibility of equilibration between cis- and trans-cyclooctenes was considered to ascertain the validity of the results of the labeling studies. The fact that the trans-octene formed from cis- β -D-24 showed no loss of deuterium indicated that there was no cis-cyclooctene \rightleftharpoons trans-cyclooctene isomerization.

A significant observation for the cyclooctyl studies was that cis-cyclooctene was not formed exclusively by an anti mechanism. The labeling in the products from cis- β -D-24 indicated that about half the cis-cyclooctene formed from the undeuterated 24 was by a syn elimination.

Studies involving bicyclic compounds^{19,20} led to the value of 1.86 for the syn mechanism. Relatively small quantities of deuterium uptake by the tertiary amine leaving group (less than 6% for norbornyl and 13% for bicyclo[2.2.2]heptyl compounds) indicated an ylid mechanism (Scheme V) for part of the syn elimination, but such a mechanism did not appear to be the major route.

Scheme V



Since all three of the values of k_H/k_D were approximately the same, the authors assumed that the average value, about 1.84, would be adequate for the estimation of syn elimination taking place for the cycloalkyl systems. By assuming that $k_{\text{syn}}/(\text{syn } k_H/k_D) + k_{\text{syn}} + 2k_{\text{anti}} = 100$ (k_{syn} and k_{anti} are relative rate constants) and letting $k_{\text{syn}}/(\text{syn } k_H/k_D) = \% \text{olefin-d}_0$, the authors estimated the $\% \text{syn}$ mechanism for the elimination of unlabeled cycloalkyl ammonium hydroxides, their results being listed in Table I.

Since the olefin products were all necessarily cis, the data indicated that both syn and anti mechanisms take place. For these smaller rings, the mixed processes indicated that all the protons on the β -carbon could be removed, in contrast with the supposition of Sicher *et al* for larger alicycles that only one proton on each β -carbon was removed for both syn and anti mechanisms. The significantly small degree of syn elimination for the cyclohexyl elimination was considered due to severe eclipsing in the syn transition state. Such interactions for the other ring systems, as demonstrated by structural models, were apparently not as significant, so that noticeable syn elimination was not unexpected.

Table I.⁴ Hofmann Eliminations of cis-2-d₁ Cycloalkyl Ammonium Hydroxides

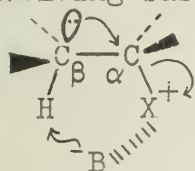
Ring Size	Conditions	%Olefin-d ₁ ^a	%Olefin-d ₀ ^a	Calc. % <u>syn</u> Elim. of 18-d ₀ ^b
Four	Dry, 50°	69	31	90
Five	Wet, 110°	86	14	46
Six	Wet, 110°	99	1	4
Seven	Dry, 50°	89	11	37
Seven	Wet, 110°	91	9	31

^aValues were corrected for isotopic purity of 97% in deuterated primary amine precursors. ^bCalculations were based on syn k_H/k_D = 1.84. Errors were estimated at about $\pm 5\%$.

Comparison of 3,3-dimethylcyclopentyl-N,N,N-trimethylammonium hydroxide (19) with cyclopentyl-N,N,N-trimethylammonium hydroxide (18, n=5) provided insight on the importance of eclipsing strain in small ring systems. Whereas the unsubstituted cyclopentene was formed by approximately 46% syn elimination, 4,4-dimethylcyclopentene was formed by about 76% syn elimination.

TRANSITION STATE CONSIDERATIONS

Sicher and his coworkers^{11,16} expanded the basic model for the syn transition state suggested by Ingold,²¹ theorizing a "double inversion" transition state (25) involving base assistance for the departure of the leaving group. Bond stretching at the β -carbon must be assumed relatively significant for such a high electron density to develop back-side to the base.



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Although an E1 mechanism has been observed for certain especially stabilized quaternary-ammonium compounds, data is available which suggests that such a mechanism is not general.³ Hofmann elimination of N,N,N-trimethyl-1,2,2-triphenylethylammonium-1-¹⁴C hydroxide gave less than 0.4% of the phenyl migration product, indicating no significant E1 or E1-like mechanism. Severe steric interactions must be considered, however, for compounds such as 5 α -cholestan-6 β -yltrimethylammonium iodide, which decomposes rapidly, possibly by an E1-like mechanism, because of interactions involving the leaving group, the 19-methyl, and the 4-methylene groups.

An E1cb, or carbanion, transition state was not considered significant for the cycloalkyl eliminations. The 100% retention of deuterium for certain olefins^{17,18} and the lack of observable deuterium in the bicyclic compounds^{19,20} led Coke and workers to suppose that no significant E1cb elimination occurred, although low k_H/k_D values did seem to indicate carbanion-like character in the transition states.⁴ In addition, Bunnett and coworkers²² observed no deuterium exchange for the eliminations of open-chained 2-hexyl halides and brosylate using CH₃ONa in methanol. Some special systems,² however, show deuterium exchange at the reacting position, and an E1cb mechanism may be presumed.

An ylid mechanism has been proposed for the syn eliminations of quaternary-ammonium compounds, but little or no deuterium incorporation into the trimethylamine by-product has been the general case. Cyclic²³ and bicyclic^{20,23} compounds studied gave small amounts of deuterated amine, but the non-ylid mechanism apparently accounted for much more of the observed products of syn elimination. Straight-chain compounds studied by Sicher and group¹³ showed behavior indicative of a syn elimination, but no deuterium incorporation was observed for trimethylamine. An ylid mechanism may, however, be favorable if the hydrogen to be eliminated is shielded from external attack by the base and is open to attack by the anion formed at one of the N-methyl groups.²⁴

In general, then, although the mechanism of syn elimination may involve a transition state with a high degree of carbanion character, the syn mechanism, like the anti, seems to be E2.

Despite evidence that steric influences of the reactants and of the environment affect the path of elimination,²⁵⁻²⁸ steric factors do not always play a significant role. Bunnett and coworkers,²² for example, in their studies with 2-hexyl halides

and brosylates, have suggested that steric factors are of little importance to the overall course of reaction except when large β -substituents are present.

CONCLUSION

Eliminations induced by strong bases have been shown to take place by both syn and anti elimination mechanisms. A tendency for syn elimination to trans-cycloolefins and for anti elimination to cis-cycloolefins has been suggested by comparative-rate and deuterium-labeling studies, although mixed products may be produced by each mechanism. Syn eliminations, in general, proceed by an E2 mechanism, although the transition state may have some degree of carbanion character.

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BIOLOGICAL OXYGENATION OF UNACTIVATED METHYLENE GROUPS BY SPOROTRICHUM SULFURESCENS

Reported by Jerome J. McDonald

December 9, 1968

Aside from the synthesis of complex and very large molecules, which still escapes organic chemists, microorganisms can perform on small molecules modest reactions which have yet to be duplicated in the laboratory. One of these reactions is the biological oxygenation of unactivated methylene groups which has been widely exploited for the past several years.¹ Quite recently the oxygenation of cyclic alcohols, amides, and heterocyclic amides by the mold Sporotrichum sulfurescens has received attention. Sufficient data have been gathered to permit the recognition of some requirements for the substrate to be oxygenated and the possible prediction of the position of oxygenation in untried molecules.

CYCLOALKANOLS

Fonken and coworkers first studied the oxygenation of monocyclic alcohols.² A large-scale, growing culture of S. sulfurescens was inoculated with a solution of cyclododecanol, and the medium was incubated, with aeration, for three days. The products extracted from the filtered medium with methylene chloride included diols, hydroxyketones, and diones. The purified mixture was oxidized to a mixture of diones with Jones' chromic acid reagent.³ The mixture of diones was resolved into three components: cyclododecane-1,6-, 1,7- and 1,5-diones in decreasing, unreported yield. Cyclotridecanol was oxygenated under the same conditions, and after oxidation with Jones' reagent yielded cyclotridecane-1,7-dione with a small amount of the 1,6-dione. Cyclotetradecanol yielded mainly the 1,6-dione.

The same procedure sufficed for the proof of structure of all these diones. A dione was subjected to Baeyer-Villiger oxidation⁴ with peroxytrifluoroacetic acid. Alkaline hydrolysis of the resulting mixture of lactones gave a natural fraction containing glycols and an acidic fraction of hydroxy acids and dibasic acids. The glycols were identified by vapor phase chromatography. Some acids were isolated directly while, following treatment with diazomethane, the methyl esters of others were identified by glpc.

Because cyclododecane was not hydroxylated, the hypothesis was advanced that the substrate must contain an electron rich group which functions in attachment of the substrate to the enzyme.² Once the substrate has been attached to the enzyme, oxygenation proceeds at a methylene carbon about 5.5 Å away from the electron rich center, determined from a Dreiding model of cyclododecanol. Dunitz and Prelog have determined the conformation of cyclododecane in the crystalline state as a plane formed by carbon atoms 1, 4, 7, and 10, with the other skeletal atoms alternating above and below this plane.⁵ Assuming that cyclododecanol retains this conformation in solution, and more importantly at the enzyme surface, then measurements on the Dreiding model from a hydroxyl group in either position on any one of the three carbon types show a large number of 5.5 Å spacings to the C-6 carbons, a lesser number to the C-7 carbon, and few to the C-5 carbon. This situation parallels the relative yield of products.⁴

CYCLOALKYLAMINES

The same products are isolated from the oxygenation of either cyclododecylamine or N-acetylcyclododecylamine: N-acetyl-6-oxocyclododecylamine and N-acetyl-7-oxocyclododecylamine.⁶ These keto-amides were transformed into the known² cyclododecane diones in a five-step procedure which involves the deamination of the N-nitrosoacetamide to form an ester.⁷ Evidently N-acylation is a necessary prerequisite to microbiological hydroxylation since a number of organisms which fail to acetylate or hydroxylate cyclododecylamine readily hydroxylate its acetamide. Nor does S. sulfurescens hydroxylate cyclododecylamine in a medium which does not allow acetylation of the amine.⁶ The requirements for the electron rich group needed for attachment of the substrate to the enzyme are further illustrated by cyclohexanol and N-acetylcyclohexylamine. While neither is hydroxylated, cyclohexyl N-phenylcarbamate is converted to 4-hydroxycyclohexyl N-phenylcarbamate.² The benzamide, benzylcarbamate, and p-toluenesulfonamide of cyclohexylamine are converted to the corresponding

4-hydroxy compounds. Fonken and coworkers attribute the binding of these derivatives to the enzyme to the increased "lipophilicity" of the side chain.⁶

The conversion of N-benzoylcycloheptylamine to N-benzoyl 4-hydroxycycloheptylamine follows a stereospecific course. After oxidation to the ketone with Jones' reagent, the bioconversion product showed $[\alpha]_D^{+65}$. The benzylcarbamate and the p-toluenesulfonamide of 4-oxocycloheptylamine showed very little or no optical activity.⁶

The benzamide and tosylamide of cyclooctylamine were converted by *S. sulfurescens* directly to a mixture of the corresponding 3- and 4-oxo compounds.⁶ The increased conformational mobility of medium and large carbocyclic rings may be the prerequisite for the direct conversion of cyclododecanol, cyclododecylamine, and derivatives of cyclooctylamine to diones and oxo-derivatives.

The relative effects of ring sizes and conformation on biological oxygenation has been investigated with N-cyclohexyl-N-cyclopentylacetamide and N-cycloheptyl-N-cyclohexylacetamide. In each case, only the larger ring was hydroxylated and in the 4-position, as expected. The rationalization of the microorganism's preference for the cycloheptyl ring over the cyclohexyl ring could lie in the greater number of 5.5 Å spacings between the carbonyl oxygen to the two equivalent methylene groups in the conformationally more mobile cycloheptyl ring. Only one ring of N,N-dicycloheptyl- and dicyclohexylacetamide was hydroxylated. The significance of this monohydroxylation is unknown, particularly in the light of the dihydroxylation of N-benzoyl-N-methyladamantanamine.

ADAMANTANAMINES

The hydroxylated compounds in Figure 1 are the products of the bioconversion of the corresponding acylated adamantanamines. The amide carbonyl, by rotation of the C-N alkyl and amide bonds, can take positions as far as 6.3 Å from and as close as 4.5 Å to one of the three equivalent C-4 carbons of the adamantane skeleton. On the other hand, the maximum and minimum distances from the C-2 carbon are 4.2 and 2.4 Å. Since the 5.5 Å distance postulated to be necessary is outside this range, hydroxylation should not occur at the C-2 carbon. Indeed no products hydroxylated at C-2 were isolated.

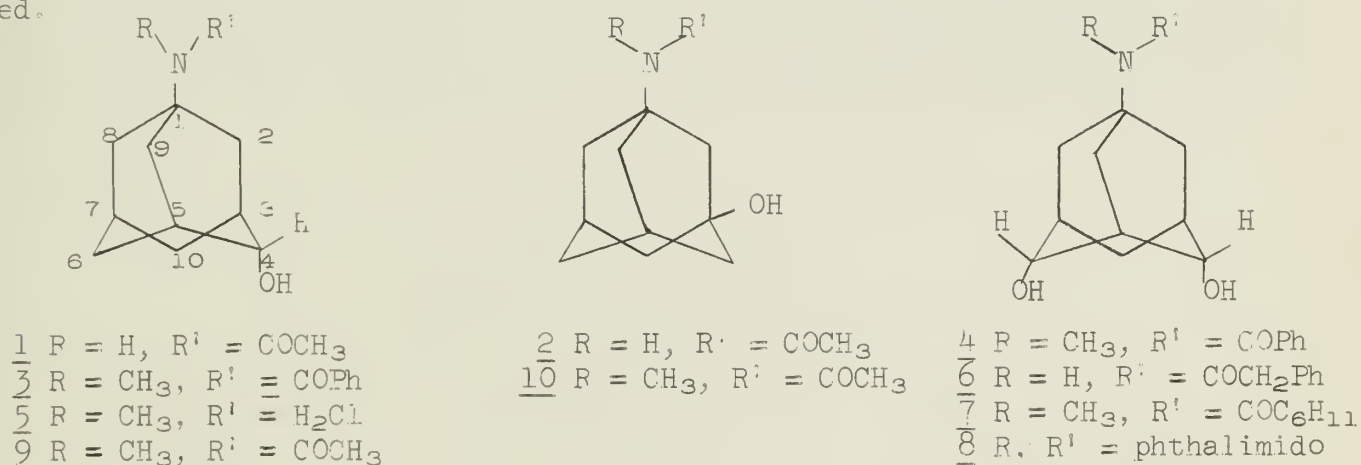


Figure 1

Hydroxy-amides 1 and 2 were both formed during the oxygenation of N-acetyladamantanamine, the former greatly predominating. Compound 1 could be oxidized with Jones' reagent to a keto-amide while compound 2 was unaffected. The keto-amide could in turn be reduced with NaBH₄ to an easily resolved, equal mixture of 1 and its epimer. This transformation, while shedding no light on the orientation of the hydroxyl, rules out C-2 as the site of hydroxylation.

While a mixture of 3 and 4 was isolated from the fermentation of N-benzoyl-N-methyladamantanamine, 3 could be converted to the diol 4 by further incubation with *S. sulfurescens*. Thus, 3 and 4 have one hydroxyl group in common. This hydroxyl group must also be of similar orientation to that of hydroxy-amide 1. Since both 1 and 3 can be transformed into the identical hydrochloride 5, the formation of a cyclic sulfite proves the similar orientation of the two hydroxyls in 4 and establishes that all the hydroxyls of amides 1, 3, 4, and 5 have the α -configuration, as shown through

their common link, N-methyladamantanamin-4 α -ol hydrochloride (5). Herr and coworkers use the designation α to refer to the 4-substituent as being trans to the C-1 reference group in an adaptation of steroid nomenclature.⁸

The nmr spectra of diol 4 and of its cyclic sulfite eliminate the possibility of a 2,4-diol. The chemical shift (δ) for the two hydroxyl protons consists of a symmetrical signal at 5.38 ppm in DMF-d₇. The two methine protons on the hydroxyl carbons show a symmetrical signal at 3.93, while the corresponding absorption for the cyclic sulfite is also symmetrical at 4.68 ppm.

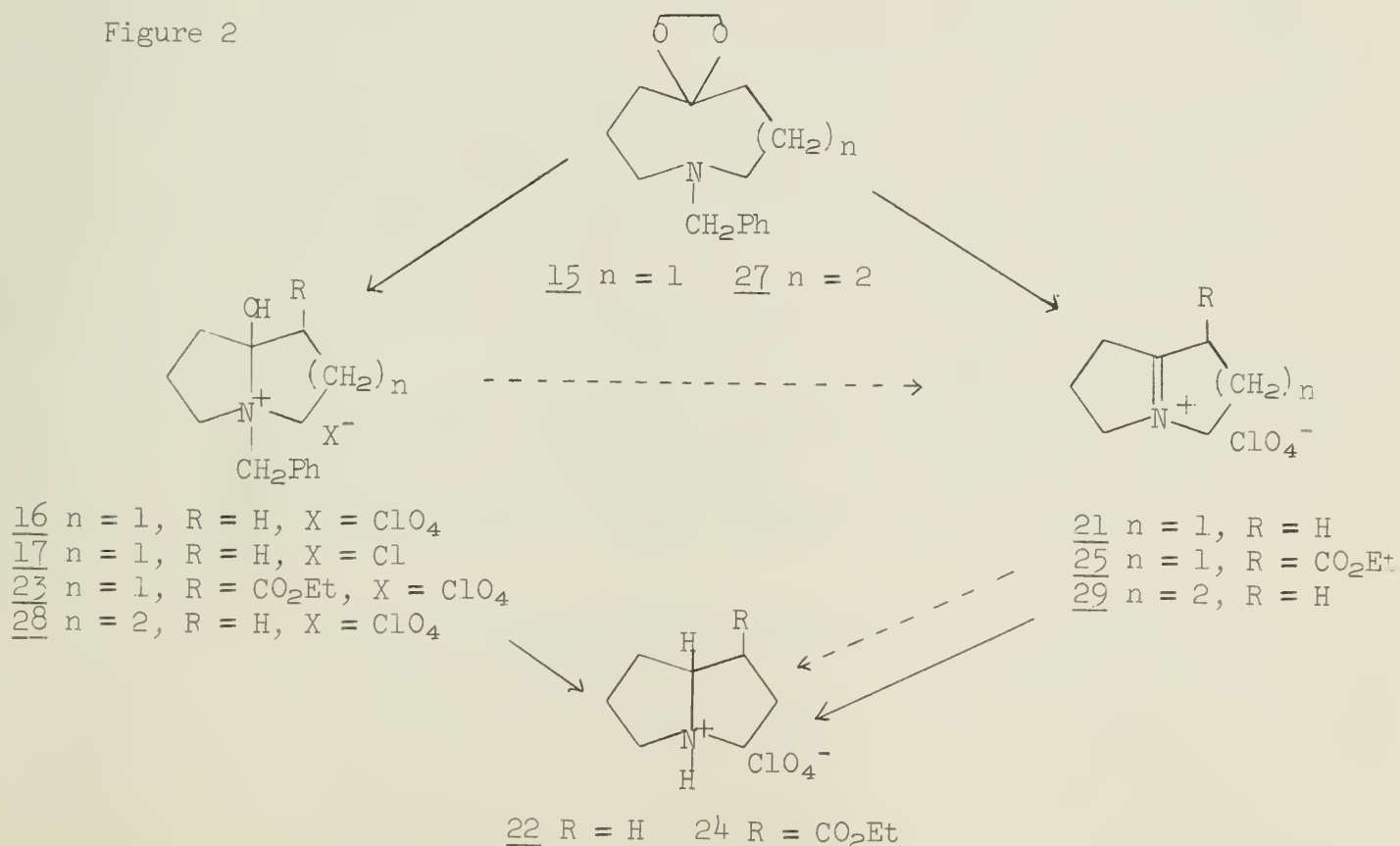
The formation of the diols 4, 6, 7, and 8 testifies to the greater attraction of the larger acyl group to the enzyme. The influence of the larger group is not merely in attraction, however. The formation of both C-4 and C-3 alcohols (1, 2, 9, 10) of adamantanamines with the smaller acetyl group shows that the acetyl group must possess less stereospecific capability of orienting the substrate at the surface of the enzyme.

AZACYCLOALKANES

The bioconversion of azacycloalkanes observed by Johnson and coworkers⁹ provides further confirmation of the proposed enzyme-substrate model.² Bioconversion of 1-benzoylpiperidine yielded 1-benzoyl-4-piperidinol. Both 1-benzoyl- and 1-p-toluenesulfonylhexamethylenimine gave the corresponding 4-hydroxy products isolated as 1-benzoyl- and 1-p-toluenesulfonylhexahydro-4H-azepin-4-one (11 and 12). The azepin-4-ones were related by replacement of the benzoyl group of 11 with the tosyl group. In addition, tosylazepine 12 was synthesized directly by ring expansion of 1-tosyl-4-piperidinone with diazomethane. The 3H-azepin-3-one was a minor product of the bioconversion of 1-benzoylhexamethylenimine alone. It was identified by the downfield shift in the nmr spectrum of methylene protons located between a carbonyl group and an amide nitrogen.

Bioconversion of 1-benzoylheptamethylenimine gave, after oxidation with Jones' reagent, 1-benzoylazacyclooctan-5-one (13) and 1-benzoylazacyclooctan-4-one (14). The ketal of 13 was reduced with LiAlH₄ to the corresponding N-benzyl derivative 15. When this compound (15) was hydrolyzed with perchloric or hydrochloric acid, a transannular reaction occurred to give the hydroxyhexahydropyrrolizinium salts 16 and 17, respectively. Both 16 and 17 could be reversibly transformed into the

Figure 2



monocyclic 1-benzylazacyclooctan-5-one (18). The infrared spectra of 16, 17, and 18 are consistent with earlier observations of Leonard and coworkers,¹⁰ with the exception of the hydroxyl band of the hydrochloride 17, which was transformed into a series of weak bands at lower wave number in Nujol. The hydroxyl absorption of 16 occurs at 3290 cm^{-1} . Both carbinol-ammonium salts 16 and 17 could be acetylated with acetic anhydride to the corresponding bicyclic acetates 19 and 20. Recently Leonard and Klainer achieved the transformation of 16 \rightarrow 19 with ketene and noted that 19 serves as a powerful acetylating agent.¹¹ The physical data of both research groups for 16 and the corresponding acetate 19 are in very good agreement.

The azacyclooctan-4-one product from 1-benzoylheptamethylenimine was transformed to a ketal-amine, the benzoyl group was reduced to benzyl, and the ketal group was hydrolyzed to give 1-benzylazacyclooctan-4-one which showed only a slight transannular interaction with a carbonyl band at 1700 cm^{-1} (versus 1675 cm^{-1} for the 5-one).

When the ketal-amine 15 was first hydrogenolyzed and then hydrolyzed with perchloric acid, the hexahydropyrrolizinium salt 21 resulted. Salt 21 could be reduced with NaBH_4 to the saturated hexahydropyrrolizinium perchlorate 22.¹² Leonard and Sato have shown the feasibility of the direct transformation 16 \rightarrow 22, which would complete the cycle shown in Figure 2. In their recent synthesis of the pyrrolizidine alkaloid (+)-isoretronecanol,¹³ the treatment of ethyl 4-benzyl-8-hydroxyhexahydropyrrolizinium-1-carboxylate (23), prepared by the transannular reaction of the corresponding amino-ketone in perchloric acid, with palladium-on-carbon resulted in the uptake of 2 mole-equivalents of hydrogen to give ethyl (+)-isoretronecanolate perchlorate (24) directly. The hexahydropyrrolizinium carboxylate (25) was very likely the intermediate formed by dehydration after hydrogenolysis of the benzyl group.

The bioconversion of 1-benzoyloctamethylenimine results in 1-benzoylazacyclononan-5-one (26) and 1-benzoylazacyclononan-4-one. The cyclononanone 26 can undergo the same transformations as 13 to form the ketal-amine 27, the hydroxyoctahydroindolizinium salt 28, and the hexahydroindolizinium salt 29.

AZABICYCLOALKANES

Since 3-benzoyl-3-azabicyclo[3.3.1]nonane (30) is ~~compound 13~~ ^{1-benzoylheptamethylenimine} constrained by a carbon bridge, one might expect some degree of stereoselectivity in its oxygenation. The only product isolated from the bioconversion of 30 in 63% yield, however, was 3-benzoyl-endo-3-azabicyclo[3.3.1]nonan-6-ol (31).¹⁴ The assumption that 31 is in the chair-chair conformation has found support in the literature.¹⁵ The endo assignment is supported by the nmr spectrum of 3-benzyl-3-azabicyclo[3.3.1]nonan-6-ol (32) formed by LiAlH_4 reduction of 31. The signal for the methine proton of the hydroxylated C-6 of 32 has a half-band width of 8 Hz at $\delta 3.98$, which is characteristic for an equatorial carbinol proton.¹⁶ Support for the position of hydroxylation at C-6 comes from oxidation of 31 to a ketone (33, $\nu_{\text{C=O}} 1705\text{ cm}^{-1}$), which picks up only three deuterium atoms on equilibration in CH_3OD with CH_3ONa . When ketone 33 is reduced with NaBH_4 , the sole product is the isomer of 31. The hydroxyl group of this isomer must be in the equatorial position since attack of borohydride on 33 is predicted to come from the less hindered endo, or axial side.

The bioconversion of 3-benzoyl-3-azabicyclo[3.2.2]nonane yields 3-benzoyl-endo-3-azabicyclo[3.2.2]nonan-6-ol (34) and 3-benzoyl-3-azabicyclo[3.2.2]nonan-6-one (35) in yields of 50% and 22%. The endo assignment to the hydroxyl results from the reduction of NaBH_4 of ketone 35 to an alcohol (36) isomeric with 34. The hydroxyl of 36 must be exo because, in acid, 36 undergoes acyl migration to form an amino ester. This migration is fully analogous to that of N-benzoylnor- Ψ -tropine.¹⁷

DECAHYDROQUINOLINE

Bioconversion of (+)-1-benzoyl-trans-decahydroquinoline yielded a mixture of alcohols, some of which were optically active. Therefore, trans-decahydroquinoline was resolved, and the 1-benzoyl enantiomers were converted separately by *S. sulfurescens* to the products shown in Figure 3.¹⁸ The conversion itself of (-)-38, (+)-39, and (+)-40 to ketones eliminated positions 4a, 8a and 2 from consideration as biological oxygenation sites, while examination of the nmr spectra eliminated positions 3 and 8. The ketone from 38 added three deuterium atoms after equilibration in CH_3OD with

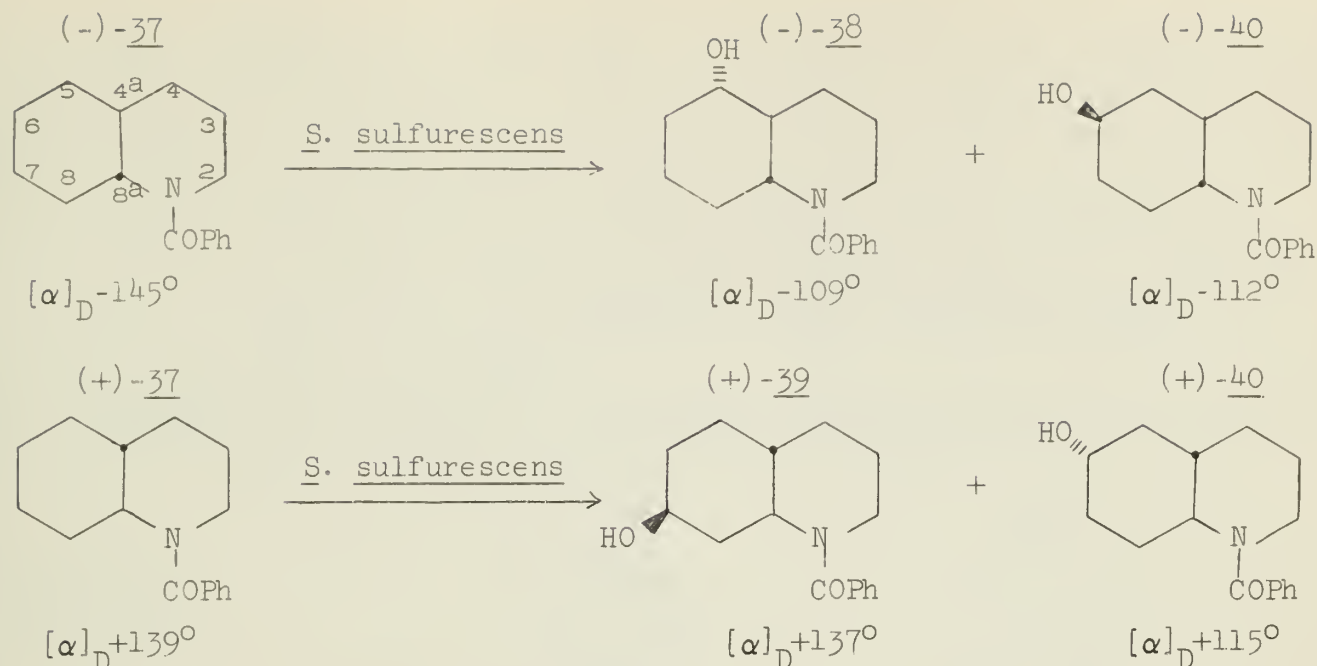


Figure 3

CH_3ONa . The total synthesis of this very same trideuterated ketone originating with (+)-5 α -hydroxy-cis-decahydroquinoline established the position of oxygenation in 38. Once the position of the hydroxyl in (-)-38 was known, the proton at position 5 was shown to be axial by the greater than 20 Hz bandwidth of its absorption in the nmr spectrum.¹¹ Supporting this assignment is the fact that the 1-benzyl-5-tosyl-trans-decahydroquinoline from (-)-38 was found to undergo the same fragmentation studied by Grob and coworkers for 1-methyl-5 α -tosyl-trans-decahydroquinoline.¹⁹ Thus, the hydroxyl at C-5 in (-)-38 must be equatorial.

With only 6 and 7 left as positions of oxygenation, (+)-39 was debenzoylated, and the solution infrared spectrum of the resulting hydroxy-amine was found to be identical with that of (+)-7 α -hydroxy-trans-decahydroquinoline, establishing the position and equatorial orientation of the hydroxyl in (+)-39. By elimination, both (+)-40 and (-)-40 had to be 6-OH compounds. When the ketone from (+)-40 was reduced with NaBH_4 , an alcohol identical in all respects with (+)-40 resulted. Since this procedure usually gives equatorial alcohols from unhindered ketones, the original orientation of the 6-OH in (+)-40 and its enantiomer is thus fixed as equatorial.

The ORD curves of the keto-amines obtained from (-)-38, (+)-39, and (+)-40 were examined to establish the absolute stereochemistry of the bioconversion products. All three showed a positive Cotton effect. The absolute configurations of (-)-38, (+)-39, and (+)-40 are uniquely defined as (4aS,5S,8aR), (4aS,7S,8aS), and (4aS,6S,8aS), respectively.

STEREOCHEMISTRY

The requirement of a 5.5 Å spacing between the electron-rich amide carbonyl and the point of hydroxylation seems to have been satisfied for all amides studied.²⁰ An acyl group attached to an amine which is a substituent on a carbon skeleton (as in the case of adamantanamine⁸ and the cycloalkylamines⁶ studied) has great rotational freedom around two N-C bonds for achieving optimum configuration. In the case of an azacycloalkane, the acyl group may prefer a planar conformation with the ring nitrogen because of conjugative interaction of the carbonyl π -system with the free electron pair of the ring nitrogen. However, Johnson,²¹ by examination of temperature dependent nmr spectra in CDCl_3 , has shown that while the acetyl group of 1-acetyl-4-methylpiperidine prefers the planar configuration at physiological temperatures, the benzoyl group shows no preference at 35°. Also, the benzoyl group of 3-benzoyl-3-azabicyclo[3.3.1]nonane shows no preference at 35°, and the benzoyl of 1-benzoyl-trans-decahydroquinoline shows no preference at any temperature.²¹ This finding is particularly important for the bicyclononane because the oxygen of the carbonyl attains its maximum distance (5.3 Å) from the site of hydroxylation only when the carbonyl is perpendicular to the plane of the ring the nitrogen is in.²⁰

A second point Johnson and coworkers feel is important in the stereochemistry of microbiological hydroxylation is the trans-orientation of resulting hydroxyl group and the amide group with each other.²⁰ In the two bicyclic compounds 31 and 34, the C-O alcohol bond is oriented in a direction opposite that of the N-C amide bond. For the hydroxy adamantane 1, the two bonds are 1,4-diequatorial with respect to a cyclohexane ring as are the same two bonds in (+)-40. However, the corresponding 1,3-diequatorial bonds in (-)-38 and (+)-39 which Johnson and coworkers label trans are usually considered to be cis with respect to the cyclohexane ring they are attached. While the C-O and N-C bonds of all the compounds of which the stereochemistry is definitely known are definitely directed opposite in space, this is probably a simple result of the 5.5 Å distance requirement.

More information on the geometry at the enzyme-substrate interface can be obtained from the diagram in Figure 4.²¹ Here the hydroxylated methylene carbon is at the

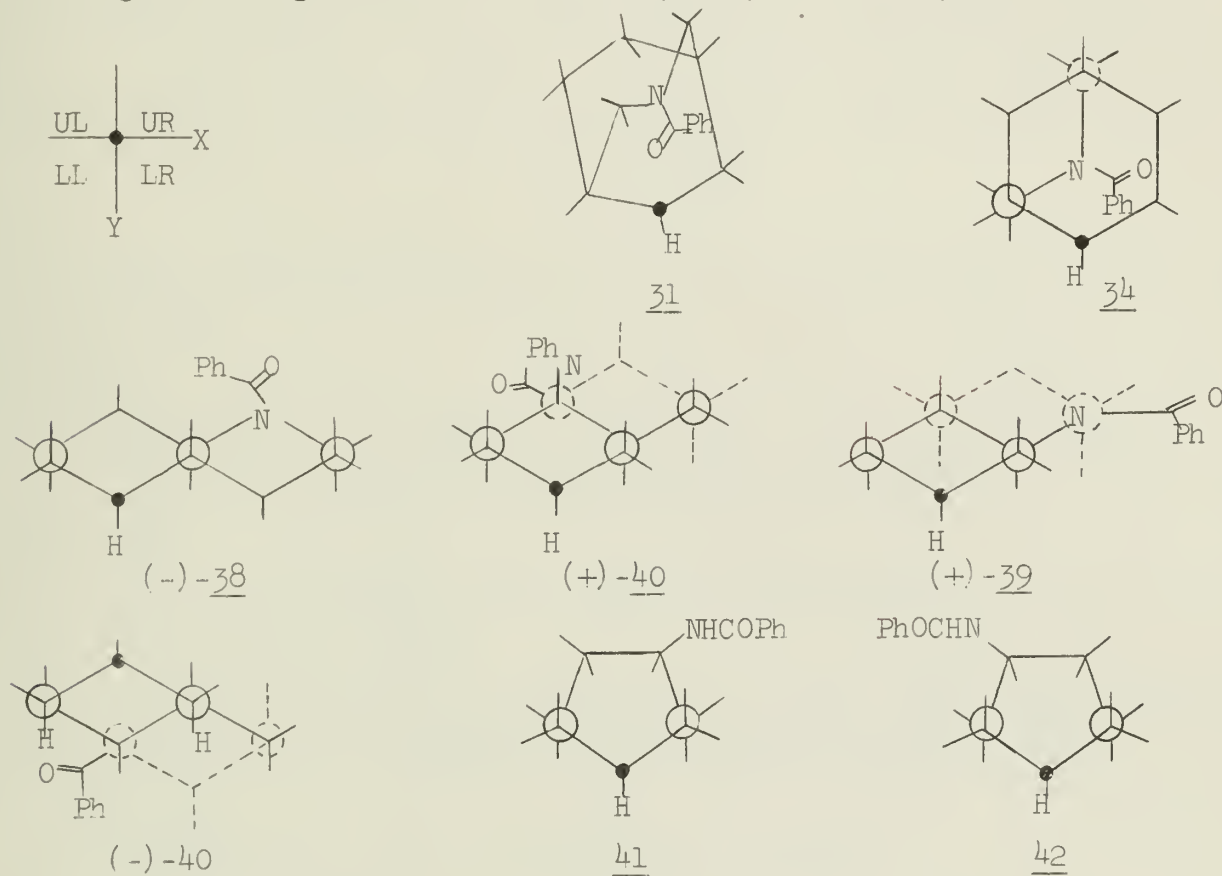


Figure 4

origin of an XYZ coordinate system. The C-O bond (heavy dot) projects out toward the viewer on the Z axis. The remaining C-H bond of the hydroxymethylene group is placed down in the vertical Y-Z plane. The grid is divided into four quadrants. As can be seen, the bicyclo compounds 31 and 34 are in both upper quadrants. The projections of the enantiomers of both 31 and 34 pictured would not be significantly different. The three decahydroquinolines (-)-38, (+)-40, and (+)-39, which are expected to give the most information about the stereochemistry of the complex because of their optical activity, project mostly into the UR quadrant. The enantiomer of (+)-40, which is a minor product of the bioconversion of (-)-37, would project into the UL quadrant in this system. Johnson and coworkers believe that the orientation of (-)-40 with the axial hydrogens α to the hydroxymethylene group projecting down parallel to the Y-Z plane is the significant one.²⁰ The enantiomer (+)-38 (known to be among the products of the bioconversion of (+)-37 but not isolated from the products of bioconversion of (+)-37¹⁸) can be oriented in the LR quadrant similarly to (-)-40. Very little (-)-39 is detected in the bioconversion of (+)-37.¹⁸ If this enantiomer is projected in a manner similar to (-)-40, the benzoyl group is also buried in the LR quadrant as is the benzoyl group of (+)-38.

The importance of these observations is that the benzoyl group of major products is in the UR quadrant or is cut by the Y-Z plane, as in (+)- and (-)-40, 31, and 34

(and their enantiomers). The orientation of the benzoyl group of the very minor products (+)-38 and (-)-39 is in the LR quadrant. The geometry of the relationship of the point of attachment of the substrate to the point of hydroxylation is now known to some degree. Using the coordinate system of Johnson and coworkers,²⁰ this reviewer predicts that the stereochemistry of the major enantiomer of N-benzoyl-4-hydroxycycloheptylamine ($[\alpha]_D^{+65}$)⁶ is probably as shown in 41, rather than in 42. The absolute stereochemistry of this product is yet to be determined.

CONCLUSION

The minimum requirements for the microbiological oxygenation of organic substrates by *S. sulfurescens* is that there be an electron rich center on the substrate to effect attachment to the enzyme and that there be approximately 5.5 Å between this center and the point of hydroxylation. A working hypothesis has been evolved for predicting the stereochemistry of the possible major products. More work is needed to form a more detailed explanation of the greater effectiveness of the larger acyl groups in forming the enzyme-substrate complex. This reviewer believes that it is possible that future work will indicate the requirement for at least one more point of attachment of the substrate to the hydroxylating enzyme.

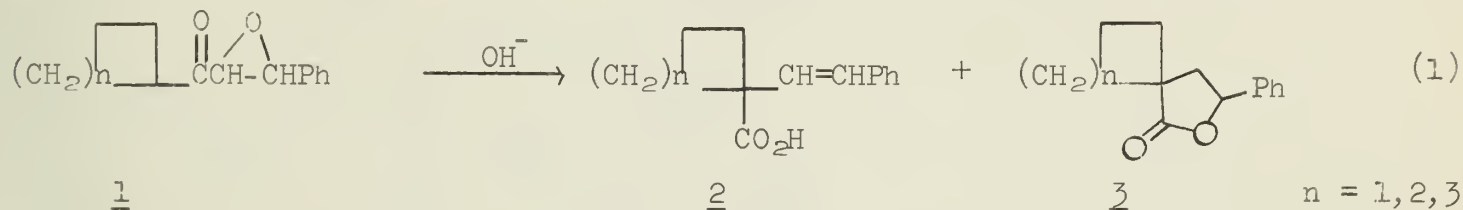
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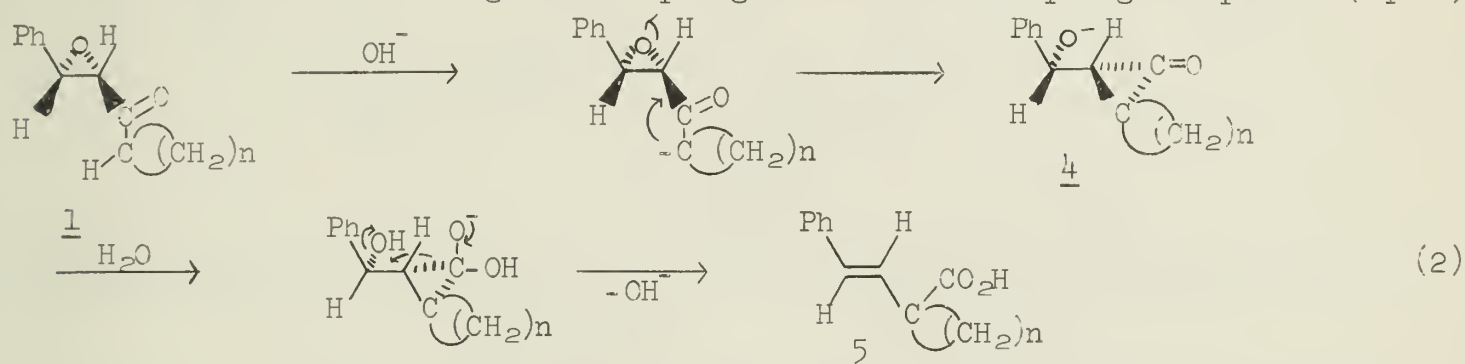
Epoxides rearrange under acidic,¹ basic,^{2,4} photolytic,^{5,6} and thermal⁷ conditions. This seminar will consider epoxide rearrangements in basic media.

α,β -EPOXY KETONES

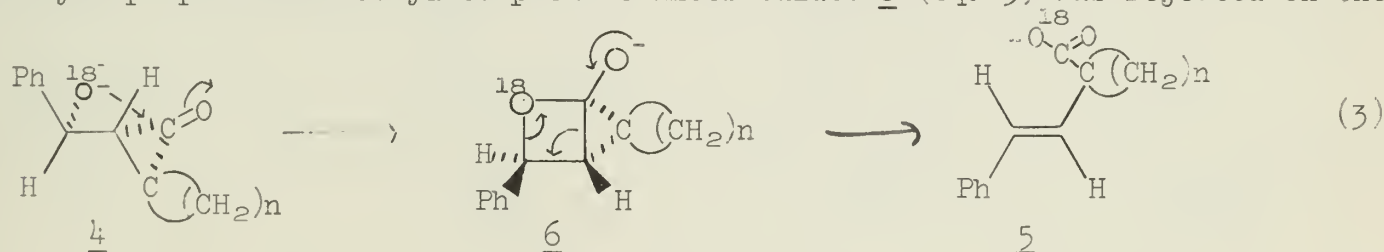
The rearrangement of α,β -epoxy ketones to benzilic acids⁸⁻¹¹ has been studied recently with a series of cycloalkyl substituted compounds.¹² An unexpected result was observed for the cyclohexyl, cyclopentyl, and cyclobutyl substituents, but not for the cyclopropyl compound. Two product types were isolated in the first three cases and were identified as the β,γ -unsaturated acids 2 and the γ -lactones 3 (eq. 1).



The mechanism proposed to explain these products is similar to those suggested by Loftfield¹³ for the Favorskii rearrangement of 2-chlorocyclohexanone and other α -halo ketones, by Kende¹⁴ for the related rearrangement of α,β -dihalo ketones, and by Achmad and Cavill¹⁵ for the rearrangement of pulegone dibromide or pulegone epoxide (eq. 2).

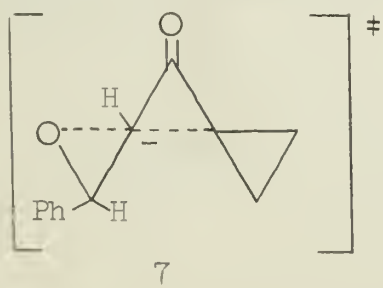


An alternate mechanism which involves attack by the alkoxide anion of intermediate 4 on the cyclopropanone carbonyl to produce intermediate 6 (eq. 3) was rejected on the basis



of an oxygen isotope labeling experiment. No labeled oxygen was retained in the product.¹²

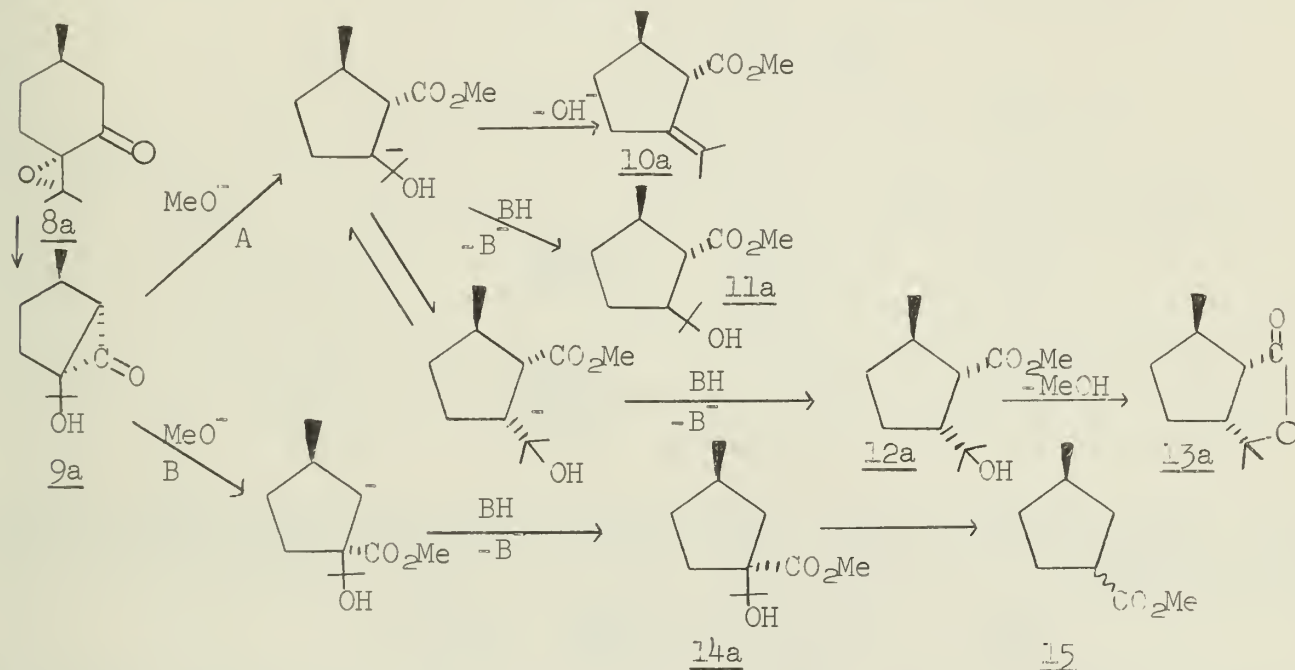
That the cyclopropyl epoxy ketone does not undergo the same rearrangement is attributed first to the strain involved in the transition state (7) leading to the analogous cyclopropanone intermediate, and secondly to the reduced acidity of the cyclopropyl proton α to the carbonyl relative to the other cycloalkanes. This latter reasoning follows from the work of Walborsky¹⁶ which showed that optically active 2,2-diphenylcyclopropyl nitrile underwent exchange in deuterium methoxide nearly 10^3 times faster than it underwent racemization. This retention of carbanion asymmetry suggested an energy barrier to rehybridization of the cyclopropyl carbanion from a hybridized orbital to a p-orbital. Thus, the cyclopropyl carbanion will not be stabilized by the adjacent carbonyl, which requires p-orbital hybridization of the carbanion, whereas the other cycloalkyl protons will be stabilized by enolate delocalization. Hence, the cyclopropyl α -proton is less acidic than the



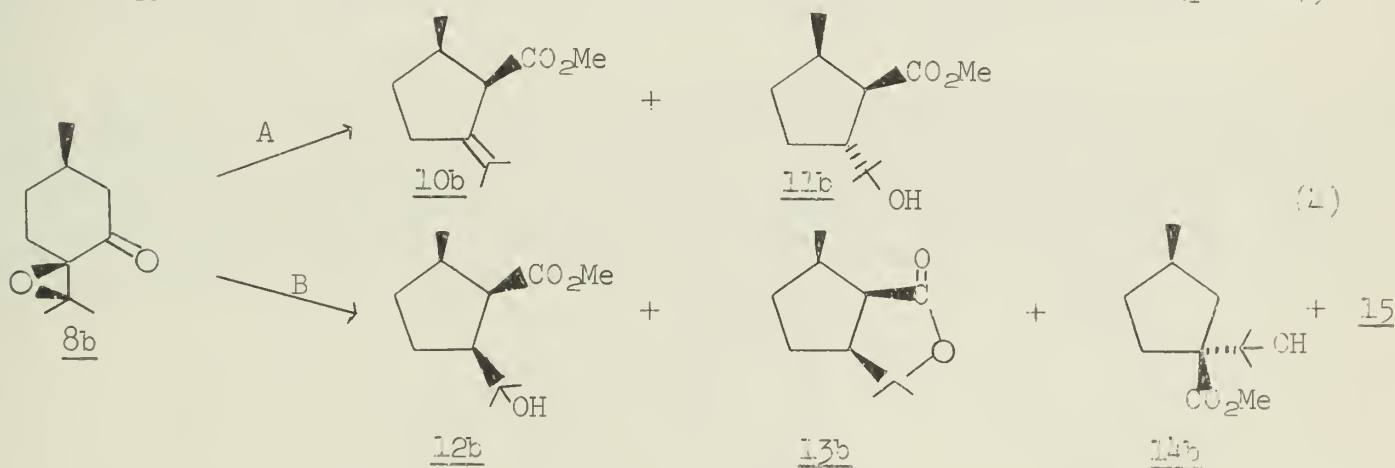
other cycloalkyl α -protons which form enolate anions.

The stereospecific Favorskii rearrangement of pulegone oxide has been studied recently in an effort to determine the stereochemistry of the epoxide stereoisomers.^{17,18} The Favorskii rearrangement of α -halo ketones to carboxylic esters is believed to proceed via a cyclopropanone intermediate in nonpolar solvents.^{14,19,20} However, only a few examples of Favorskii rearrangements with α,β -epoxy ketones are known.^{21,22} Reaction Scheme I illustrates the possible products which may be formed from one stereoisomer of pulegone oxide. The other pulegone oxide isomer would give stereoisomeric products (eq. 4). Judging from other Favorskii rearrangements,¹⁴ base catalyzed

Reaction Scheme I



opening of 9a would be expected at the least substituted α -carbon atom (path B),



yielding 14a. However, products from the "abnormal" cyclopropanone cleavage (path A) predominated, and 10a and 13a were isolated in good yields.²³ Since the stereochemistry of these products is known,²³ the assignment of the oxide configurations was possible.

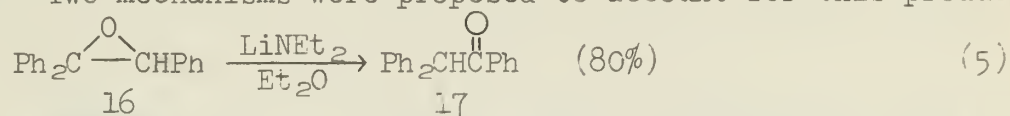
Table I

Oxide Isomer	Product Yield (%)					
	<u>10a</u>	<u>11a</u>	<u>13a</u>	<u>10b</u>	<u>11b</u>	<u>15</u>
"M"	29	50	-	-	-	21
"N"	12	-	21	11	33	15

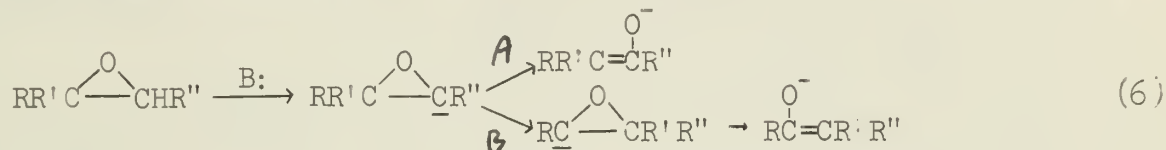
The initial oxide stereoisomers are denoted in Table I by "M" and "N", each with its characteristic melting point and spectral data. The rearrangement of "M" is remarkably stereospecific, and although the products from "N" have undergone some epimerization, the stereospecificity is evident. Thus, oxide "M" is 8a and oxide "N" is 8b.

α-ELIMINATION CARBANION MECHANISM

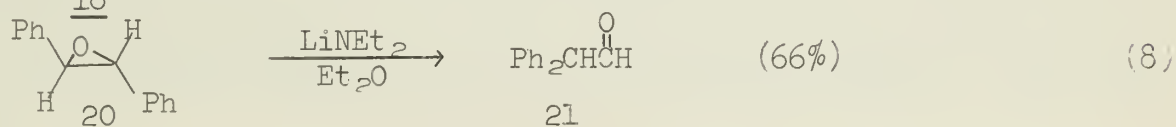
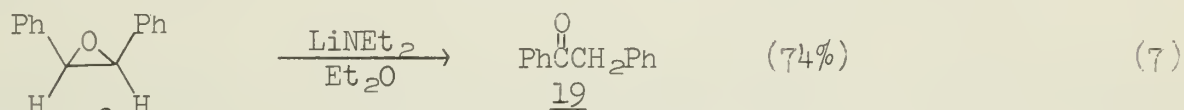
A carbonyl is not necessary to activate epoxide rearrangements. Triphenylethylene oxide undergoes rearrangement when treated with lithium diethylamide to give benzhydryl phenyl ketone (eq. 5).²⁴ Two mechanisms were proposed to account for this product



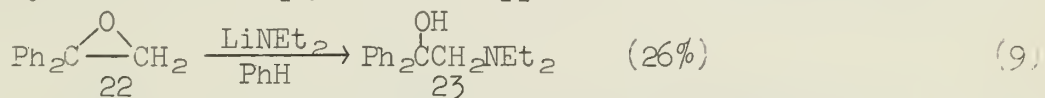
(eq. 6). Studies on the rearrangement of cis- and trans-stilbene oxides revealed a



distinct preference for path B in a stereospecific manner (eqs. 7 and 8).²⁴ These



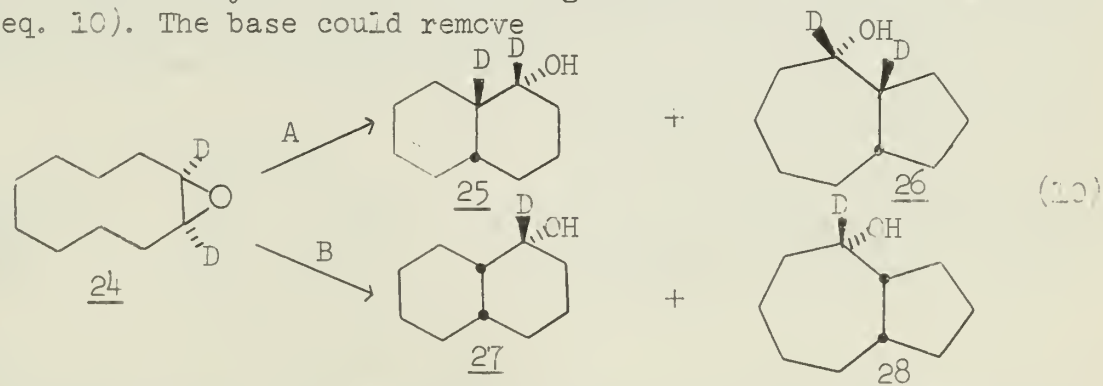
results suggest cis migration and frontal attack upon an anionic center. The rearrangement of 1,1-diphenylethylene oxide (eq.9) lends support to a carbanion mechanism.



The protons involved here are not benzylic and hence are less acidic. Consequently, only the bimolecular reaction occurs.

α-ELIMINATION CARBENOID MECHANISM

The effect of strong bases such as lithium diethylamide and phenyllithium on cis- and trans-cyclooctene oxides has been studied.²⁵ Similar results were obtained from the rearrangements of cis- and trans-cyclodecene oxides.²⁶ The complex product mixtures obtained could be explained only by considering transannular effects. The detailed mechanism was clarified by deuterium labeling studies.²⁷ Two mechanisms were considered likely (eq. 10). The base could remove

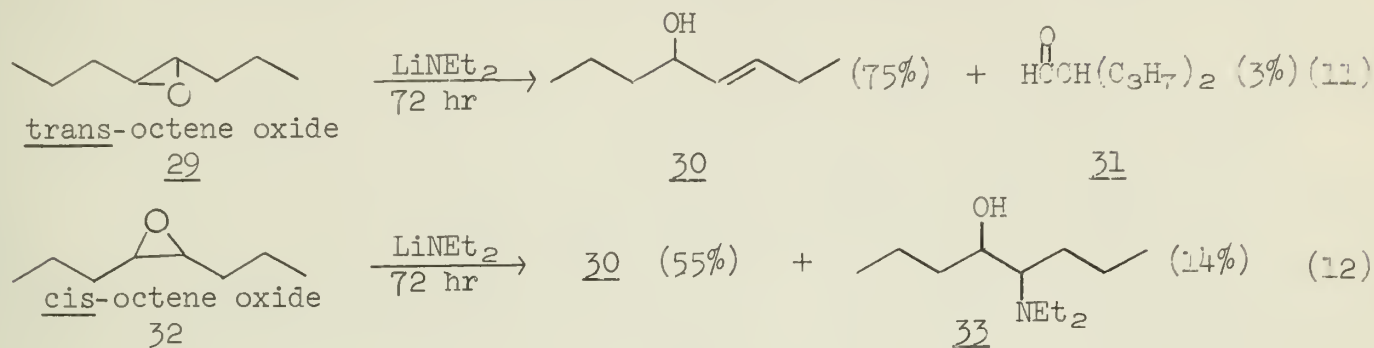


a proton from carbon atom C-6 or C-7 across the ring from the epoxide followed by opening of the epoxide ring by intramolecular attack of the carbanion so formed (path A). Alternatively, the base could remove a proton from the epoxide ring followed by carbon-oxygen bond cleavage to form a carbenoid intermediate which could then insert into a carbon-hydrogen bond across the ring (path B). The products formed are single stereoisomers. The bicyclic products formed in the reaction retained only 0.93-0.96 atom of deuterium per mole of the 1.78 atoms of deuterium originally present per mole of 24; thus, path B, the carbenoid mechanism, seems to prevail. Furthermore, cis-cyclooctene oxide with deuterium at C-5 and C-6 was found to retain all of the deuterium in the rearranged products formed,²⁷ which rules out a path A-type mechanism for this

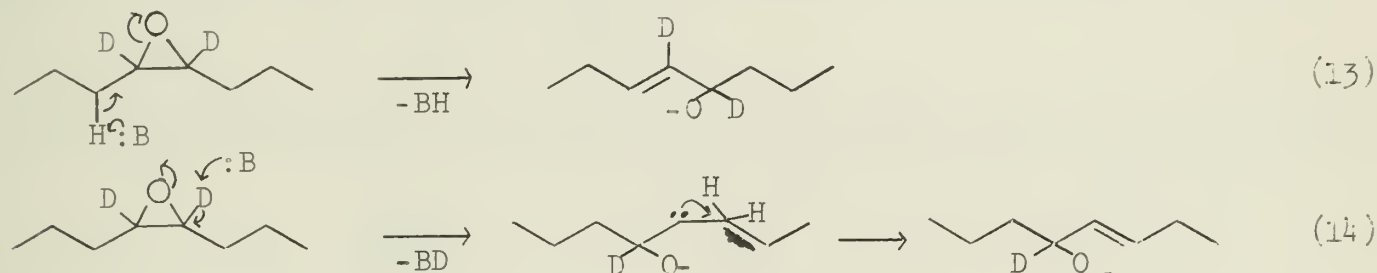
compound.

β-ELIMINATION MECHANISM

The effect of lithium diethylamide on octene oxides has been studied (eqs. 11 and 12).²⁸ The formation of the allylic alcohol might proceed by either of two

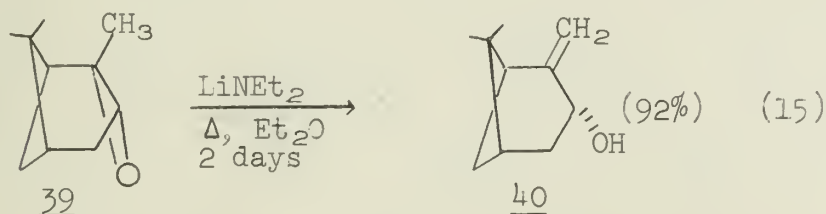


mechanisms. The base could remove a proton from the carbon beta to the oxygen atom to give a carbanion followed by opening of the oxirane ring (eq. 13): the β-elimination pathway. Alternatively, the base could remove a proton from the oxirane ring to give a carbene, as in the cycloalkene oxide studies, followed by carbene insertion into the adjacent carbon-hydrogen bond (eq. 14): an α-elimination pathway. Deuterium



labeling allowed a distinction to be made between these two mechanisms. The trans-5-octene-4-ol obtained from cis- and trans-4-octene oxide-4,5-d₂ were found by mass spectrometry to have retained 88 and 92% of both deuterium atoms, respectively. Thus, the carbanion mechanism must operate almost exclusively with both oxides.

Allylic alcohols have also been obtained by the lithium diethylamide treatment of 1-methylcycloalkene oxides (five-through eight-membered rings),²⁹ α-pinene oxide (eq. 15), β-diisobutylene oxide, cyclopentene oxide, and cyclohexene oxide.³⁰ The

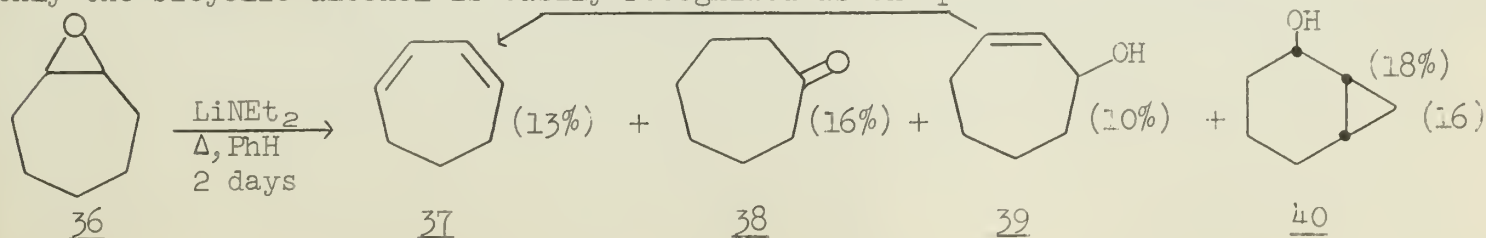


treatment of 2-methyl-2-butene oxide with potassium *t*-butoxide in dimethylsulfoxide,³¹ and of cis- and trans-cyclododecene oxides with *n*-butyllithium^{32,33} similarly gave rise to allylic alcohols.

INTERMEDIATE EXAMPLES

Some epoxides rearrange with little apparent preference for either α- or β-elimination.

Cycloheptene oxide gave four products in approximately equal amounts (eq. 16).³⁰ Only the bicyclic alcohol is easily recognized as the product of a carbenoid intermediate



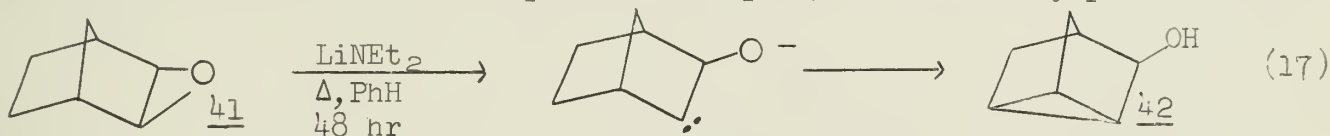
It is formed to the complete exclusion of the epimeric alcohol. The cycloheptadiene may have been formed from the 2-cycloheptenol, since resubjecting the allylic alcohol to the reaction conditions established that it was partially converted to 37.

α - VS β -ELIMINATION

The results thus far discussed allow the formation of a self-consistent mechanistic framework.³⁰ The decisive feature which appears to control the balance between α - and β -elimination is the stereoelectronic requirement for β -elimination. Molecules conformationally capable of attaining the preferred transition state for β -elimination, i.e., a trans, coplanar arrangement³⁴ of one of the epoxide carbon-oxygen bonds and a proton on an adjacent carbon atom, apparently adopt this mechanistic pathway. Recent work has shown that β -elimination can occur from a cis, coplanar arrangement as well.³⁵⁻³⁷ Epoxides which undergo β -elimination include, among others, the 4-octene oxides, the five-, six-, and twelve-membered cycloalkene oxides, and α -pinene oxide. Each of these compounds may easily adopt conformations with the desired elimination geometry, or something sufficiently close to it. The tendency for medium-ring epoxides to generate insertion products is attributable to their inherent torsional strain and transannular nonbonded interactions which strongly influence the conformational preferences of these compounds and inhibit the normal β -elimination process. In these situations, the generally less favored mechanism, α -elimination, prevails. Qualitatively, this is supported by the observation that, in general, more drastic conditions are required to effect the rearrangement of medium-ring epoxides. With increased ring size, the cycloalkene oxides have sufficient mobility that their behavior is identical to that of the acyclic compounds.

SPECIAL SITUATIONS: β -ELIMINATION PREVENTED

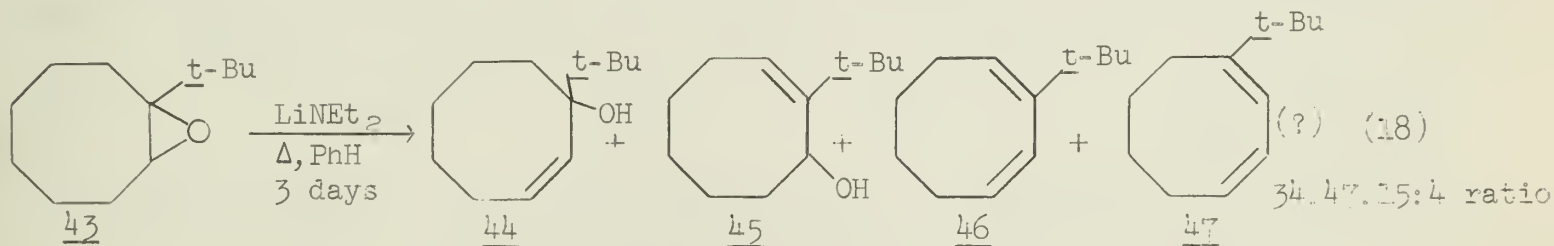
Norbornene oxide provides a noteworthy example of the occurrence of transannular insertion when β -elimination is not permitted (eq. 17).³⁸ The only product formed



in this reaction is nortricyclanol (42). When this reaction is run with lithium cyclohexylamide-N-d, in the presence of cyclohexylamine-N,N-d₂, the starting material can be recovered in 35% yield with 76% incorporation of two atoms of deuterium per mole.³⁹ This result strongly suggests an equilibrium between the epoxide and a metallated intermediate prior to carbenoid formation.

SPECIAL SITUATIONS: α -ELIMINATION PREVENTED

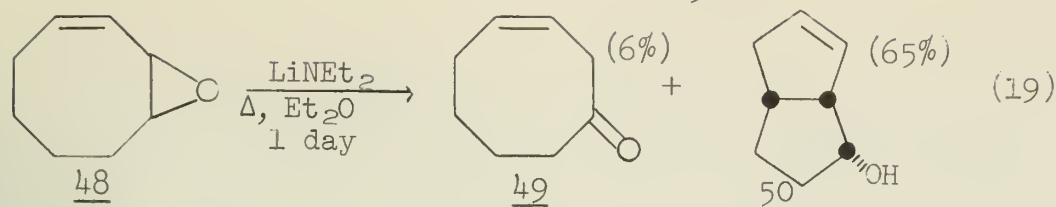
The treatment of 1-*t*-butylcyclooctene oxide with lithium diethylamide gave rise to four products (eq. 18).²⁹ The same two allylic alcohols were obtained as the major



products when *t*-butyllithium was used as the base. The steric influence of the bulky *t*-butyl substituent must sufficiently destabilize the conformations which allow transannular insertion that the transannular hydrogens never approach the reaction site.

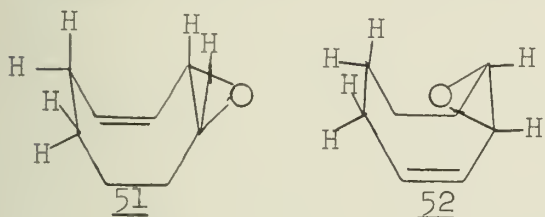
THE CARBENOID INSERTION REACTION

The results from the cyclooctene oxide studies²⁵ support the idea of α -elimination followed by a stereospecific carbenoid insertion into a transannular carbon-hydrogen bond.²⁷ Similar results are observed with cis- and trans-cyclodecene oxides.²⁸ Treatment of 3,4-epoxycyclooctene with excess lithium diethylamide gave rise to two products (eq. 19).⁴⁰ The double bond has had little effect on the course of the reaction in comparison with the cyclooctene oxide results except to direct formation of the carbenoid center to the allylic carbon atom. Of the two conformations which bring the correct transannular proton near the reactive site, conformation 51 predicts

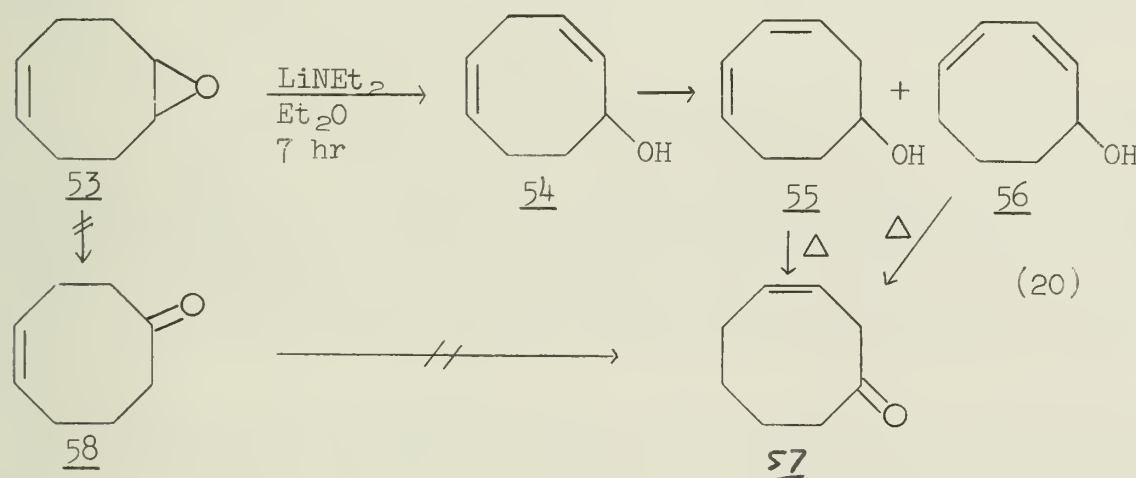


formation of the observed alcohol, whereas 52 would produce the epimer. The preference for 51 over 52 must arise from the steric

repulsion between the oxygen and the hydrogen(s) across the ring. This same destabilization applies to the respective carbenoid formation transition-states, thereby making 51 the only important conformer in determining the reaction product. Alternatively, the preference for reaction from 51 over 52 may be attributed to an inherent stereoelectronic requirement which necessitates approach of the transannular carbon-hydrogen bond from the side of the reactive carbon atom away from the departing oxygen.

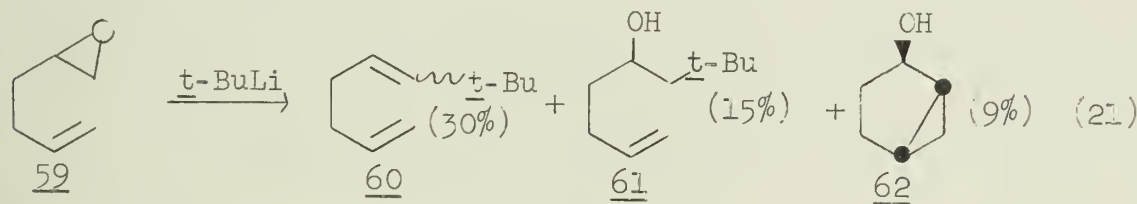


A more complicated reaction occurred with 5,6-epoxy cyclooctene (53). The initial product formed suffered base-catalyzed isomerization and the products of this isomerization were thermally converted to an additional product (eq. 20).⁴⁰ Presumably, the



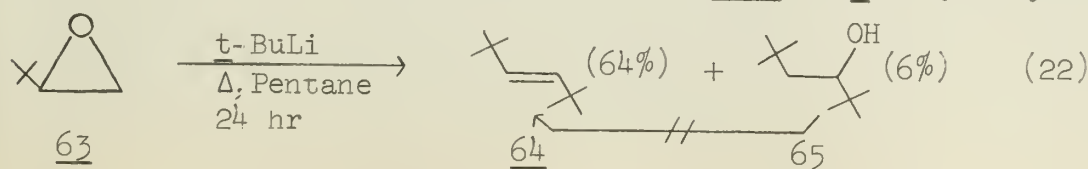
double bond in the middle of the ring sufficiently reduces the availability of transannular hydrogens that β -elimination to an allylic alcohol will occur. The direct rearrangement of 53 to a ketone would be expected to yield 4-cyclo-octenone (58) rather

than the observed 3-cyclooctenone (57). Control experiments showed that 58 did not isomerize to 57 under the reaction conditions and must not therefore be formed in the reaction. The unsaturated alcohols produced in this reaction do undergo thermal conversion to 57, presumably by 1,5-hydrogen migrations.⁴¹ The treatment of 5,6-epoxy-1-hexene with *t*-butyllithium gave rise to three products (eq. 21).⁴² The formation



of the bicyclic alcohol appears to require an α -elimination carbenoid mechanism with subsequent addition to the

neighboring double bond rather than insertion into a neighboring carbon-hydrogen bond as previously observed. The stereospecific formation of this alcohol requires that the carbenoid reaction occur only from one of the two obvious conformations of 59. There are no particularly good steric grounds which would predict this result. Possibly the epimer of 62 not shown is formed but epimerizes under the reaction conditions to give 62. The unexplained stereospecificity does not allow the formulation of any meaningful conclusions relative to the intermediacy of a ring-opened carbenoid species. Compound 61 is the expected nucleophilic addition product.² The mixture of olefins (60) probably does not arise from dehydration of 61, but from carbenoid decomposition of 59, since *t*-butylethylene oxide, when treated with three equivalents of *t*-butyllithium in refluxing pentane gave mainly *trans*-di-*t*-butylethylene (eq. 22).⁴³ The

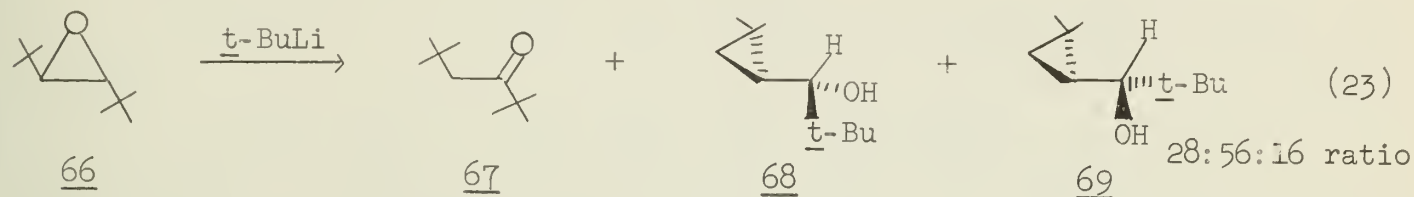


intermediacy of 65 in the formation of 64 was ruled out as 65 gave no dehydration

products under the reaction conditions.

No products attributable to β -elimination are formed in eq. 21. Since no conformational restrictions should hinder this reaction pathway, the capabilities of *t*-butyllithium must substantially differ from lithium diethylamide and must promote carbenoid reactions, presumably by favoring the metalation reaction.

Three products were obtained from the rearrangement of *trans*-di-*t*-butylethylene oxide with *t*-butyllithium (eq. 23).⁴² The formation of the diastereomeric alcohols



probably occurs by carbenoid insertion into a carbon-hydrogen bond of the adjacent *t*-butyl substituent. In contrast to all previous experiments, these insertion products are formed nonstereospecifically. Presumably, the particular diastereomer formed here depends on the rotational conformer which the reacting methyl group of the *t*-butyl substituent has adopted at the time of the reaction.

The lack of stereospecificity in equation 23 does not seem to be relevant to the question of a concerted carbenoid reaction mechanism⁴⁴ versus a stepwise mechanism with a ring-opened intermediate. The stereospecificity observed in the medium ring compounds suggests the possibility of a concerted mechanism,²⁵ although a rapid, stepwise mechanism is possible. ~~A similar conclusion follows from the results observed in equation 24.~~ Decisive information³⁰ bearing on this question might be provided by determination of the deuterium isotope effect caused by replacing one of the reacting hydrogens with deuterium in a reaction proceeding by carbon-hydrogen insertion.

CONCLUSION

Epoxides with relatively acidic protons, such as those adjacent to carbonyl or phenyl substituents, undergo carbanion initiated rearrangements in basic media. Unactivated epoxides may adopt any of three types of rearrangement mechanisms in basic media: α -elimination carbanion, α -elimination carbenoid, and β -elimination. The major factor which determines which mechanism will be operative is conformational effects. Molecules which can adopt favorable conformations of the reacting atoms will undergo β -elimination; those molecules which cannot will undergo α -elimination. The distinction between the α -elimination carbanion and the α -elimination carbenoid mechanisms is experimentally tenuous. However, the carbenoid mechanism can explain all the results requiring α -elimination whereas the carbanion mechanism cannot. The use of lithium diethylamide apparently does not favor one mechanism over another; the use of *t*-butyllithium favors the α -elimination carbenoid mechanism. The stereospecificity observed in transannular insertion reactions argues in favor of a concerted mechanism, but definite experimental evidence to establish this point is not yet available.

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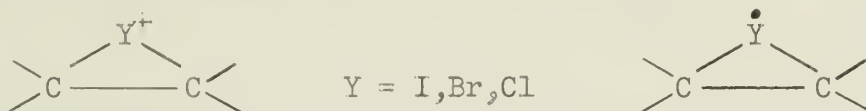
BRIDGED HALOGEN RADICALS

Reported by Richard J. Arhart

December 16, 1968

INTRODUCTION

While the concept of ionic halogen bridging between two adjacent atoms is well established, the analogous radical halogen bridging remains controversial. The production of bridged halogen radicals has been approached along two lines: (1) the



radical addition of addenda such as HBr, Br₂, or I₂ to olefins and (2) the radical halogenation of alkyl halides. The first approach involves the free radical addition of a halogen atom to the olefin to yield a β -haloalkyl radical which may form the cyclic bridged halogen radical. The second approach involves hydrogen abstraction beta to the halogen of the alkyl halide and possible formation of the bridged halogen radical. Most of the evidence for radical halogen bridging has been obtained from stereochemical studies of the products derived from these two approaches. The seminar will deal only with bridging across carbons.

RADICAL ADDITIONS TO OLEFINS

Addition of HBr to 1-Halo-cycloalkenes. Goering, Abell, and Aycock¹ first proposed the bridged halogen radical when they observed that the free radical addition of hydrogen bromide to 1-bromocyclohexene and 1-methylcyclohexene yielded the cis-1,2-disubstituted cyclohexanes exclusively. They felt that a classical open free radical could not account for the stereospecific trans addition of hydrogen bromide to form the thermodynamically less stable cis-1,2-disubstituted cyclohexane. The bridged bromine radical would require entering hydrogen bromide to transfer hydrogen trans to the cyclic bridge, thereby achieving stereospecific trans addition.

Later, a second mechanism was proposed which involved the formation of a pi-complex between hydrogen bromide and the olefin.² Subsequent attack by a bromine radical would occur from the side opposite the complexed hydrogen bromide, resulting in stereospecific trans addition and production of another bromine radical from the complexed hydrogen bromide.^{3,4} To test this mechanism ether was added to the reaction mixture, since it should complex preferentially with hydrogen bromide and prevent pi-complex formation with the olefin. However, complete stereospecificity was maintained, suggesting that the pi-complex was not a requirement for stereospecific trans addition. A third mechanistic possibility involved bromine radical attack upon the double bond from the axial direction to yield an open β -bromocyclohexyl radical.⁵ Rapid transfer of a hydrogen atom trans to the bromine occurring faster than conformational changes would account for the trans addition and cis product.^{3,4}

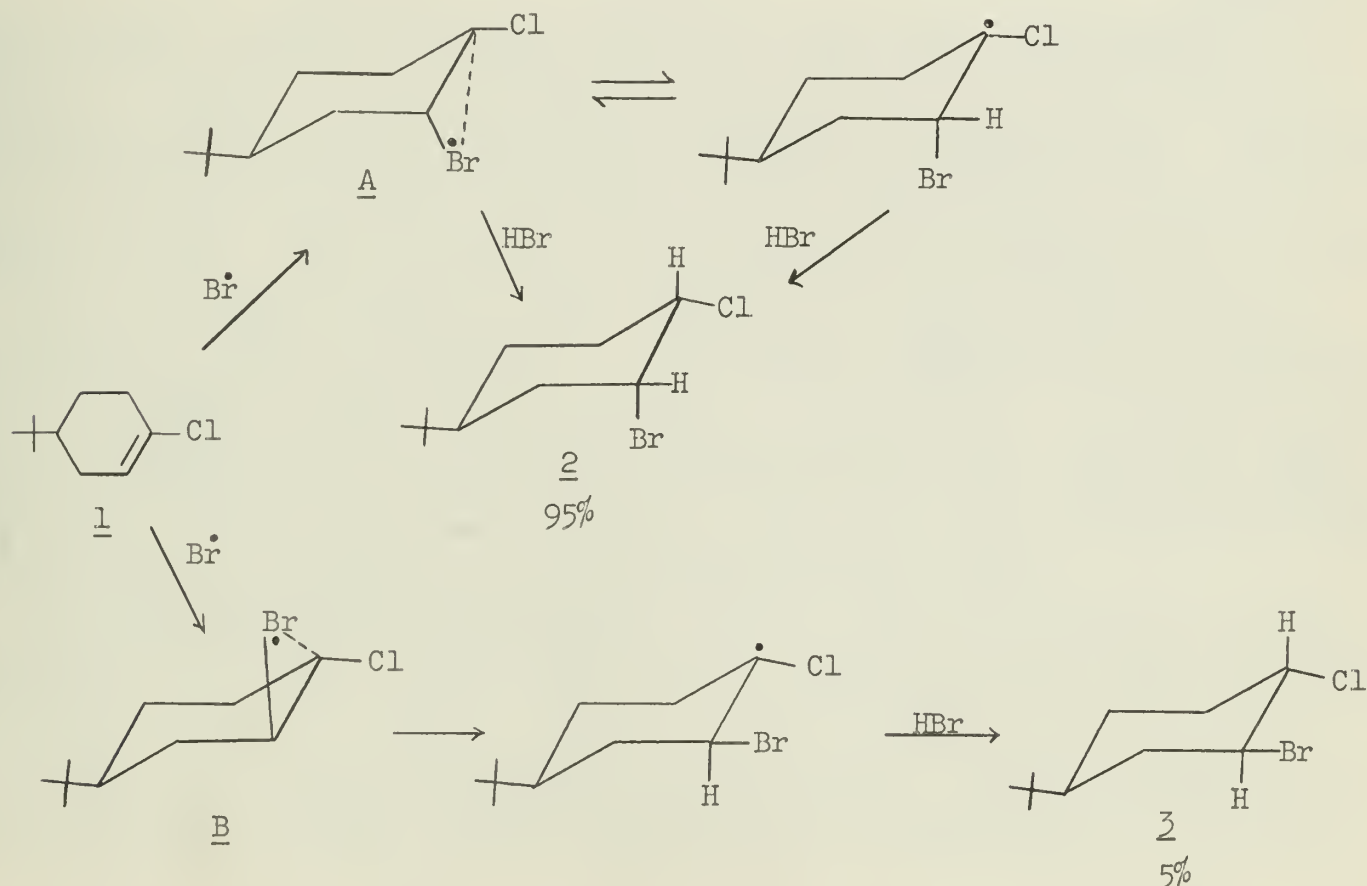
Abell and Chiao⁶ carried out the free radical addition of hydrogen bromide to 1-bromocyclobutene, 1-bromocyclopentene, and 1-bromocycloheptene. The product ratios cis:trans 1,2-dibromocycloalkanes were determined from gas chromatographic and infrared spectral data and are as follows: dibromocyclobutane 79:21, dibromocyclopentane 94:6, and dibromocycloheptane 91:6. Products of ionic addition, the 1,1-dibromides, were not observed. The 1-bromocyclohexene yielded essentially all cis-1,2-dibromocyclohexane (only 0.3% trans detected).² The variation in isomer ratios was postulated to be the result of a competition between a preference for trans addition via open radicals and a steric inhibition to formation of the resulting cis isomers. In contrast, Skell interpreted the results as indicative of a bromine bridged radical intermediate.⁷ He proposed that the non-stereospecificity indicates that the stability of the bromine bridged radicals relative to the classical open radicals may be altered by strain, so that ring opening becomes faster than trapping with hydrogen bromide.

More recently, Readio and Skell⁸ have irradiated a pentane solution of hydrogen bromide and 1-chloro-4-t-butylcyclohexene (1) at -78°. The reaction proceeded readily to give a good yield of free radical addition products 2 (95%) and 3 (5%). The stereochemistry of 2 and 3 was determined by vapor phase chromatographic,

alkaline dehydrohalogenation, nmr, and infrared analyses. Only a minor amount (2%) of the ionic product, 1,1-dihalo, was detected by gas chromatography. The presence of the *t*-butyl group precludes conformational flipping of the cyclohexane ring. A 32 fold change in hydrogen bromide concentration had no effect on the 19 to 1 ratio of 2 to 3. Although these results may be accounted for by employing only classical radicals, the authors interpreted them by assuming the presence of bridged bromoalkyl radicals. They postulate that the formation of the major adduct 2 requires initial bridging of bromine on the side of the double bond trans to the *t*-butyl group. Hydrogen abstraction opposite the bridge would occur rapidly to yield 2. However, the alternative process of bridge opening and reaction of the classical radical to give axial hydrogen preferentially is not ruled out by the results.

Initial bromine bridging on the side of the double bond cis to the *t*-butyl group would yield intermediate B. Transfer of a hydrogen atom to B would have produced cis-3-bromo-cis-4-chloro-*t*-butylcyclohexane, a product not observed. To yield 3, B must first open to a classical radical. Preferential axial hydrogen abstraction to give 3 must be explained in terms of accessibility of hydrogen bromide approach and product stability. This reasoning appears somewhat tenuous in that in one case product is formed directly from a halogen bridged intermediate A while in the other the bridged intermediate B must first open to a classical radical. From the ratio of rate constants, $k(4)/k(1) = 2.0$, for the competitive addition of hydrogen bromide to 1 versus 1-chloro-cyclohexene (4) it appears that the *t*-butyl group has no appreciable effect on the addition. Consequently, the 19 to 1 preference for formation of bridged radical A over B might appear too high. The proposed mechanism for addition is illustrated in scheme I.

Scheme I



The halogen bridging in this system can be pictured as involving unsymmetrical bridges. For example, if the halogen bridge on intermediate A were symmetrical, some formation of the 1,1-dihalide would be expected as a result of hydrogen transfer to C-3. However, unsymmetrical bridging in A maximizes the free-electron density on C-4 such that more effective use of the resonance stabilizing effect of the chlorine can take place with the result that hydrogen transfer occurs only at C-4. Stated in general terms, this electronic effect causes the bridge to be unsymmetrical in the direction which favors the more stable of the two unbridged radicals.⁸

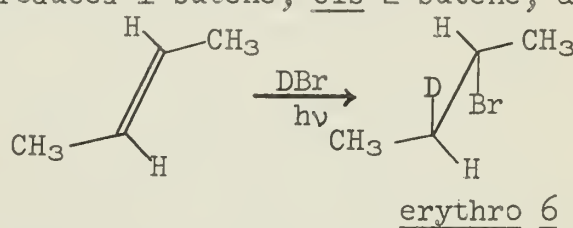
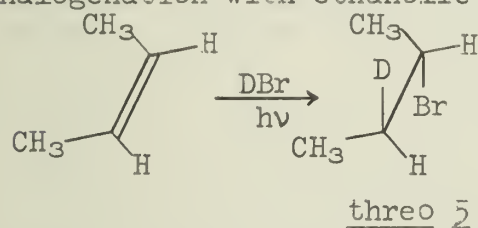
A slightly different approach to formation of a β -bromoalkyl radical was followed by Applequist and Werner,^{3,9} who observed that the brominative decarboxylation of

silver-(+)-trans-1,2-cyclohexanecarboxylate proceeded with net inversion of configuration. They proposed that the results were explained best by intermediate classical open radicals rather than by bridged radicals.

Cases of apparent sulfur bridging have been observed in the free radical addition of thiols to olefins. For example, both the addition of methyl mercaptan to 1¹⁰ and the oxidative addition of para substituted thiophenols to indene^{11,12} yielded products resulting predominantly from trans addition. Intermediate bridged sulfur radicals were postulated to control the stereochemistry of the products in both cases. Studies of sulfur bridging are important because of the analogy with halogen bridging.

Addition of DBr to cis- and trans-2-Butene. With respect to free radical additions acyclic olefins present a different stereochemical problem from that of the cyclic ones, because any intermediate formed is free to rotate about the single bond resulting from collapse of the double bond following radical attack. In addition, there exists the possibility of isomerization of the alkene through reversal of the addition step.

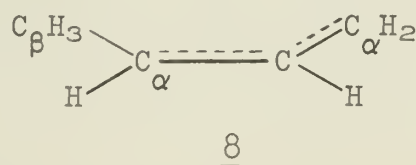
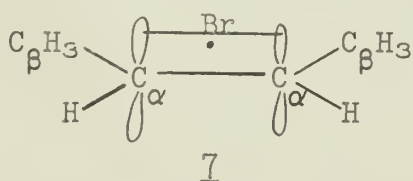
Skell and Allen^{7,13} observed a stereospecific trans addition of deuterium bromide to cis- and trans-2-butene upon illumination between -78° and -60° to yield threo (5)- and erythro (6)-3-deuterio-2-bromobutane, respectively. Alkaline dehydrohalogenation with ethanolic potassium ethoxide produced 1-butene, cis-2-butene, and



trans-2-butene. Separation of these olefins by vapor phase chromatography and infrared analysis of the 2-butenes showed that isomer intercontamination was negligible. Failure to observe isomer intercontamination proves that both hydrohalogenation and dehydrohalogenation are stereospecific trans processes. The formation of two intermediate classical β -bromoalkyl radicals that abstract deuterium from deuterium bromide faster than they interconvert by rotation about the C-C bond appears somewhat unlikely. Instead, Skell⁷ has proposed that the stereospecificity can be explained best by the formation of two intermediate bromine bridged radicals.

The stereochemistry of free radical addition to a terminal olefin has been investigated by Skell and Freeman.¹⁴ A stereospecific trans addition of deuterium bromide to trans- and cis-1-deuterio-1-hexene was observed upon irradiation to yield threo- and erythro-1,2-dideuterio-1-bromohexane, respectively. As in the 2-butene case the reaction involves two radical intermediates which are converted to their respective products faster than conversion of one to the other. Again the formation of diastereoisomeric bridged bromine radical intermediates would explain the control of stereochemistry observed during the deuterium transfer step.

Esr Study of HBr Addition to Olefins. Electron spin resonance (esr) spectroscopy has been used by Abell and Piette¹⁵ as a tool for examining the structure of the intermediate bromoalkyl radicals formed in the light-induced free radical addition of hydrogen bromide to a series of olefins and acetylenes in the solid state at 77°K. The spectra can be interpreted in terms of bridged bromine radical intermediates. For example, the spectrum obtained from the cis-2-butene -hydrogen bromide mixture during photolysis consisted of seven basic lines with a splitting of 10.8 gauss. The spectrum is consistent with the bridged symmetrical structure 7. The coupling



pattern can be explained by a hyperconjugative interaction of the unpaired electron with the six equivalent β -methyl protons. The single hydrogens on the olefinic carbons lie out of the plane of the pi electron system and would not be expected to couple significantly. The trans-2-butene -hydrogen bromide mixture also gave a basic seven line spectrum but with a splitting of 12.6 gauss. If the intermediate radicals

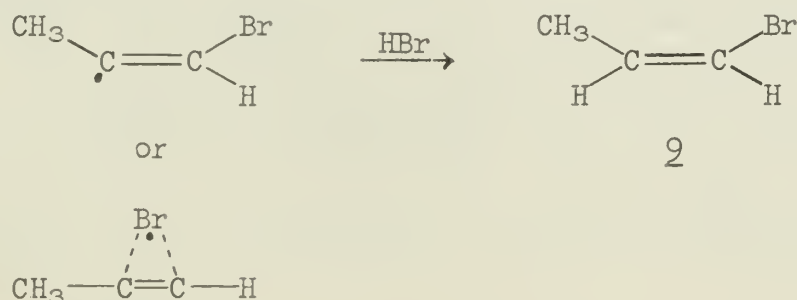
obtained from cis- and trans-2-butene were open β -bromoalkyl radicals, they would be expected to yield identical spectra because of free rotation about the C-C bond. The difference in coupling constants between cis and trans isomers illustrates that they do not yield identical intermediate radicals.

These esr results should be treated somewhat cautiously because the reactions were run in the solid state where radical lifetimes are of substantial length.¹⁶ Since all the product studies were done on reactions carried out at -78°C and above, care must be exercised in extending the results in the solid phase to those in the liquid and gas phases. In addition, Symons¹⁷ has suggested that the radicals observed by Abell and Piette could well have been delocalized allylic radicals formed by $\text{Br}\cdot$ attack on allylic hydrogen. The basic seven line spectrum reported for cis-2-butene is in reasonable accord with expectation for allyl radical 8. The unpaired electron would be distributed primarily on C_1 and C_3 , so that hyperfine coupling to three α -protons and three β -protons could account for the seven line spectrum. Implicit in this reasoning is the assumption that coupling with the "central" allylic proton is small. Consequently, the esr results of Abell and Piette cannot be taken as conclusive evidence in support of the presence of intermediate bromine bridged radicals.

Addition of Iodine to cis- and trans-2-Butene. The radical chain addition of iodine to cis- and trans-2-butene has been carried out by Skell and Pavlis¹⁸ in refluxing propane (-42°) with illumination to yield dl-2,3-diiodobutane and meso-2,3-diiodobutane, respectively. A comparable dark reaction run for several hours did not result in extensive consumption of iodine. Samples of the diastereomeric 2,3-diiodobutanes have been kept in the dark at -78° for days without decomposition; however, at room temperature upon illumination the diiodides decomposed rapidly to the respective starting olefins in better than 90% yields. Thus, both addition and elimination reactions are trans-stereospecific. Skell and Pavlis propose that this stereospecific addition is best rationalized in terms of intermediate iodine bridged radicals.¹⁸ Non-stereospecific additions would be indicative of unimolecular opening of the bridged radical to a classical radical, a process which would be in competition with the bimolecular trapping by iodine. Stereospecificity was maintained down to an iodine concentration of 10^{-5}M , indicating a remarkable stability for the iodine bridged radical.⁷

Benson, Golden, and Egger¹⁹ disagree with Skell's suggestion for the presence of bridged iodine radical intermediates. They contend that if the photocatalyzed stereospecific dehalogenations of the diiodides are concerted processes then the additions are concerted processes also. Therefore, no intermediate β -iodoalkyl radical, much less a bridged one, could exist.

Addition of HBr to Propyne. Under illumination propyne and hydrogen bromide react rapidly in the liquid phase²⁰ at -78 to -60° and in the gas phase²¹ at room temperature by a stereospecific trans radical chain process, producing cis-1-bromo-1-propene (9). The formation of a bridged intermediate radical would explain the results, since the bridged species would require donation of a hydrogen atom trans to the bromine atom.²¹ However, isomerization of a cis vinyl radical is an activated process (est. $E_{\text{act}} \geq 17 \text{ kcal./mole}$) and might be precluded under the reaction conditions. Consequently, the stability of cis vinyl radicals lessens support for a bridged intermediate radical.



HALOGENATION OF ALKYL HALIDES

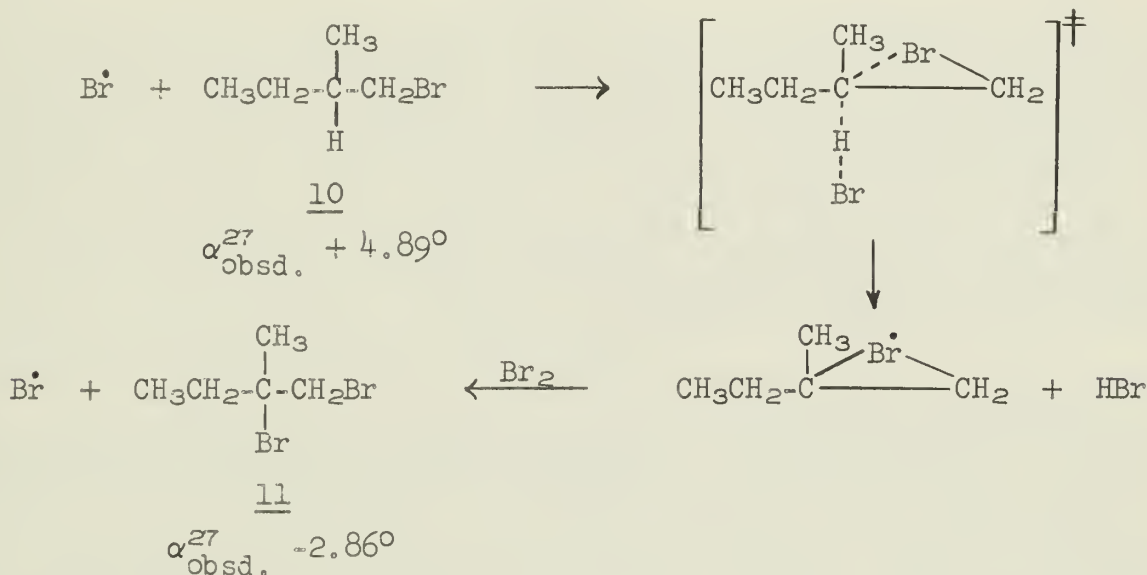
Halogenation of 1-Halo-2-methylbutane. The generalization that free radical halogenations of alkyl halides generally occur preferentially at positions removed from the halogen substituent²² is not always correct. Thaler²³ has shown that

radical photobromination of alkyl bromides proceeds in a selective manner to yield predominantly the vicinal dibromoalkanes (84-94%).

Free radicals produced at the asymmetric center in optically active compounds generally yield optically inactive products. For example, the radical chain chlorination of optically active (+)-1-chloro-2-methylbutane produces a mixture of dichlorides and inactive 1,2-dichloro-2-methylbutane when substitution occurs at the asymmetric center.²⁴ The latter observation shows that the asymmetric intermediate radical is racemized before it is converted to dichloride. In contrast, Skell, Tuleen, and Readio^{25,26} have found that the liquid phase photobromination of (+)-1-bromo-2-methylbutane (10) at 0° yields only (-)-1,2-dibromo-2-methylbutane (11) of high optical purity. Bromination of (+)-1-bromo-2-methylbutane differs from chlorination of the corresponding chloride in two important respects. First, bromination yields an optically active product while chlorination produces inactive 1,2-dichloro-2-methylbutane. Second, bromination is selective and affords only 1,2-dibromo-2-methylbutane while chlorination is a reaction of low selectivity and all possible dichlorides are produced.

The unexpected activation of C-2 suggests anchimeric assistance by the neighboring bromine atom in the transition state for hydrogen atom abstraction as illustrated in scheme II. The production of optically active dibromide product requires that the

Scheme II

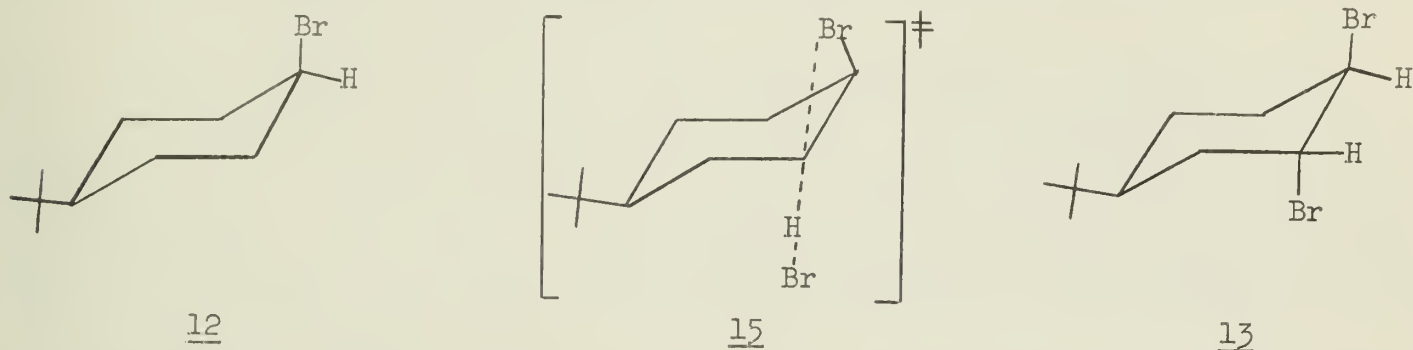


bromine atom on C-1 fix the configuration of C-2, the center of asymmetry. This control of configuration at C-2 can be described in terms of a bromine bridged radical, which is trapped by bromine faster than it opens and racemizes to the non-asymmetric classical β -bromoalkyl radical.⁷

The importance of Skell's conclusions for the radical bromination of optically active bromide 10 has been lessened by the work of Haag and Heiba.²⁷ They observed that the liquid phase photobromination of (+)-1-cyano-2-methylbutane, $[\alpha] = +7.98^\circ$, with 1M bromine proceeded with high selectivity at the tertiary carbon to yield (+)-2-bromo-1-cyano-2-methylbutane, $[\alpha] = +1.69^\circ$. The change in optical rotation upon brominating the nitrile was comparable to that observed upon brominating 10. Haag and Heiba assumed that neighboring group participation leading to a cyano bridged radical analogous to the proposed bromine bridged radical was unlikely. They proposed that reaction of the intermediate β -cyanoalkyl radical with bromine might be sufficiently fast to compete with racemization. Also the rate of trapping of a short-lived non-planar intermediate β -cyanoalkyl radical might be expected to increase if the hydrogen abstracting species is Br_2 rather than Br^\cdot , because this would place a bromine molecule in immediate proximity to the intermediate β -cyanoalkyl radical as it is formed.

In studies of the syn-anti isomerization of substituted benzophenone N-chlorimines and N-bromimines, Curtin and McCarty²⁸ observed that halogenation of cyclohexane solvent occurred under certain conditions. The possibility for formation of an intermediate diphenylimine radical $[(\text{C}_6\text{H}_5)_2\text{C}-\text{N}^\cdot]$ exists. Consequently, Haag and Heiba's assumption that a cyano bridged radical is improbable may be incorrect.

Bromination of cis- and trans-4-Bromo-t-butylcyclohexane. The presence of a bulky t-butyl group in a cyclohexane ring inhibits chair-chair interconversion of the ring. Thus the cis and trans configurations of 4-bromo-t-butylcyclohexane are conformationally pure ($\geq 96\%$), having the bromine substituent fixed in the axial and equatorial positions, respectively. The photobromination of cis-4-bromo-t-butylcyclohexane (12) yielded trans-3-cis-4-dibromo-t-butylcyclohexane (13) as the chief product ($> 90\%$) while a similar reaction with trans-4-bromo-t-butylcyclohexane (14) yielded a mixture of isomeric dibromides at a slower rate.²⁹ From competitive photobromination experiments the ratio of rate constants for the brominations of bromides 12 and 14 has been calculated to be $k(12)/k(14) \geq 15$. From these results



Skell¹⁷ postulated that the axial bromide 12 assists in the transition state for hydrogen abstraction (15) by bridging. The bridged intermediate would be attacked from the axial direction at C-3 opposite the bridge to yield 13 in accordance with the "diaxial rule" for ring openings of epoxides. The alternate equatorial attack at C-4 to yield the diequatorial bromide is a higher energy reaction path.

Anchimeric assistance is not observed in hydrogen abstractions from the equatorial bromide 14 because a trans arrangement of hydrogen and bromine in the transition state can be obtained only after conversion of the chair conformation to a higher energy boat-like form. Therefore, bridging is unlikely because unassisted hydrogen abstractions follow lower energy paths.

It should be mentioned that an elimination-addition sequence could account for the results. This mechanistic possibility will be discussed in the following section.

Halogenation of i-Butyl and t-Butyl Halides. Photochlorination of i-butyl and t-butyl bromides at -78° with t-butyl hypochlorite yields the common product, 1-bromo-2-chloro-2-methylpropane.³⁰ A 1,2-bromine migration has been invoked to explain the rearranged product formed from t-butyl bromide. Such a 1,2-bromine rearrangement lends strong support for the presence of an intermediate bromine bridged radical.

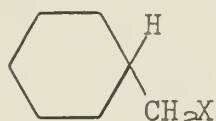
Haag and Heiba³¹⁻³³ have photochlorinated t-butyl bromide at -78° in carbon disulfide with t-butylhypochlorite. The photochlorination always yielded some of the unrearranged product, 1-chloro-2-bromo-2-methylpropane, the proportion of which increased linearly with increasing hypochlorite concentration. These results indicate that a classical β -bromoalkyl radical is a true intermediate and can be intercepted by chlorine transfer from t-butylhypochlorite. Haag and Heiba were able to scavenge free bromine atoms with allene, ultimately obtaining bromochloropropenes in 42% yield at the expense of the rearranged dihalide. Consequently, the rearranged dihalide appears to be formed, at least in part, by elimination of $\text{Br}\cdot$ from the β -bromoalkyl radical, readdition of $\text{Br}\cdot$ to the double bond so as to form the more stable tertiary radical, and chlorine transfer from t-butylhypochlorite. These results suggest that other 1,2-halogen migrations may be due to this elimination-addition sequence.

The photochlorination of t-butyl bromide in carbon tetrachloride at 24° with elemental chlorine afforded only the rearranged product, 1-bromo-2-chloro-2-methylpropane.³⁴ The elimination-addition mechanism of Haag and Heiba³¹ does not appear to be operative here because a molecule of chlorine would be expected to add quickly to any isobutylene formed by elimination of $\text{Br}\cdot$ from the intermediate radical. The formation of the product can be explained most easily by assuming the formation of an intermediate bromine bridged radical. When attacked by a chlorine atom, the bridge opens preferentially at the tertiary position because of the electron releasing ability of the methyl groups.

Photochlorination of *i*-butyl bromide under the same reaction conditions yielded three products: 1-bromo-2-chloro-2-methylpropane (59%), 1-bromo-3-chloro-2-methylpropane (33%), and 1-chloro-2-bromo-2-methylpropane (8%).³⁴ The 1-bromo-2-chloro-2-methylpropane could have resulted from attack of chlorine on a bridged radical or an open tertiary radical. However, the formation of a bridged radical here is less likely than in the case for *t*-butyl bromide because hydrogen abstraction by chlorine forms a fairly stable tertiary radical rather than a less stable primary radical. The minor product, 1-chloro-2-bromo-2-methylpropane, may have resulted from opening of a bridged radical at the primary position. But if this were the case, some 1-chloro-2-bromo-2-methylpropane would be expected from the chlorination of *t*-butyl bromide with elemental chlorine at 24°.

Juneja and Hodnett³⁴ observed that the photobromination of *t*-butyl chloride with elemental bromine at 24° was a very slow reaction which resulted in the exclusive formation of 1,2-dibromo-2-methylpropane. The mechanism of this reaction must be that of chlorine elimination to form isobutylene and subsequent addition of molecular bromine. Photobromination of *i*-butyl chloride gave only 1-chloro-2-bromo-2-methylpropane. This product is expected from the known selectivity of tertiary hydrogen abstraction by bromine. The results of Juneja and Hodnett indicate strongly that the mechanism(s) for halogenation of alkyl halides is very sensitive to structure and reaction conditions.

Halogenation of (Halomethyl)cyclohexanes. The chlorination of (bromomethyl)-cyclohexane (16a) with molecular chlorine in carbon tetrachloride at room temperature and the analogous bromination of (chloromethyl)cyclohexane (16b) by Traynham and Hines³⁵ resulted in attack largely at the tertiary position with some migration (12-15%) of the bromo substituent. The rearrangement of the 1-(bromomethyl)cyclohexyl



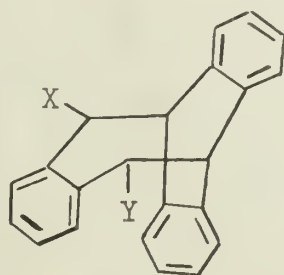
16a X = Br

16b X = Cl

radical could have resulted either from a bromine bridged radical that undergoes predominant but not exclusive attack at the tertiary carbon or by elimination of Br[•] followed by recombination of the olefin-atom pair³¹ (unexpectedly) at the tertiary carbon. However, some dichloride would be expected via the elimination-addition mechanism, but none was observed.

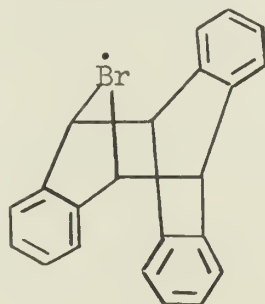
Strong evidence for anchimeric assistance by chlorine in the hydrogen abstraction step has been obtained in experiments with *trans*-4-methyl-1-(chloromethyl)cyclohexane (17).³⁵ The expected retardation by chlorine vicinal to one tertiary position should lead to preferential attack at the more remote tertiary position by bromine.²³ However, bromination of 17 produced only 4-methyl-1-bromo-1-(chloromethyl)cyclohexane. These results indicate that chlorine assists in the transition state for hydrogen abstraction by bridging.

Possible 1,5-Bromine Bridged Radicals. Cava and coworkers³⁶ observed that the bromination of 9,10-dihydro-9,10-*o*-xylyleneanthracene (18a) under free radical conditions yielded either the unrearranged monobromide 18b or the rearranged dibromide 20. The bromine atom in 18b appears to play an important part in the

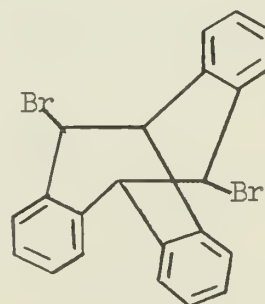


18a X = Y = H

18b X = Br, Y = H



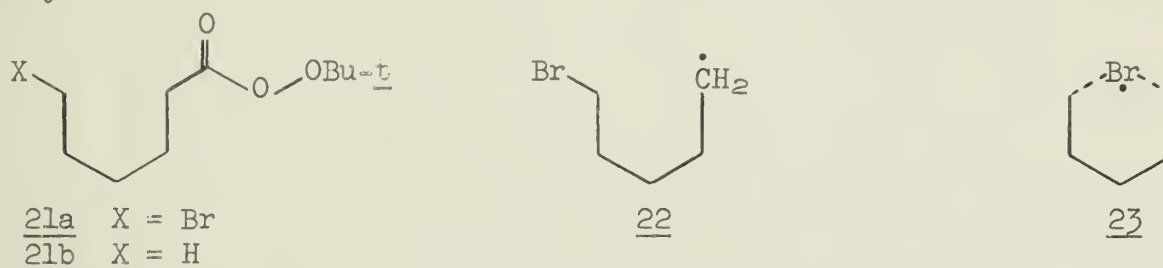
19



20

rearrangement that accompanies bromination of 18b to 20. The authors suggest that the radical formed by abstraction of a hydrogen atom from 18b is stabilized considerably by neighboring group participation of the bromo substituent. The resulting 1,5-bromine bridged radical 19 would have a geometry particularly conducive to a transoid rearrangement to the energetically more favorable structure of 20. The rearrangement leads to a resonance stabilized benzylic radical which forms 20 upon abstraction of a bromine atom. The bromine bridged radical 19 appears to slow down the bromine transfer step so that rearrangement to structure 20 becomes competitive with it. Another possibility is an electron transfer by 19 to yield a bromonium cation which undergoes rearrangement and bromine attack to yield 20.

The thermal decompositions of bromo perester 21a and the unsubstituted perester 21b under similar conditions gave comparable yields of the corresponding major products.³⁷ If the 5-bromopentyl radical 22 bridged to form 23, the reactivity of the radical should be lowered. However, there is no evidence that the 5-bromine affects the reactivity of the pentyl radical and thus the existence of 23 seems unlikely.



If the bridged radical 23 is much more stable than 22, the 5-bromine atom of perester 21a could assist its thermal decomposition via neighboring group participation. Assistance of this type should lead to a substantial rate enhancement. However, the rate of decomposition of bromo perester 21a in cyclohexane ($1.4 \times 10^{-5} \text{ sec}^{-1}$) is equal to that of unsubstituted perester 21b. Thus, both the rate and product data give no evidence for the formation of the 1,5-bromine bridged radical 23.

CONCLUSION

The production of possible bridged halogen radicals has been approached generally by either the radical addition of various addenda to olefins or the free radical halogenation of alkyl halides. The latter approach provides stronger evidence for halogen bridging. Two of the best examples in support of bridged intermediates are the bromination of (+)-1-bromo-2-methylbutane and the chlorination of *t*-butyl bromide with elemental chlorine.

The formation of intermediate bridged halogen radicals appears to be very sensitive to structure and reaction conditions. Under suitable trapping conditions the bridged intermediate can play a determining role in controlling structure and stereochemistry. Although the greater majority of the stereochemical results can be explained in terms of intermediate bridged halogen radicals, they cannot be invoked generally. Other possibilities, such as the elimination-addition sequence, exist and sometimes appear more probable.

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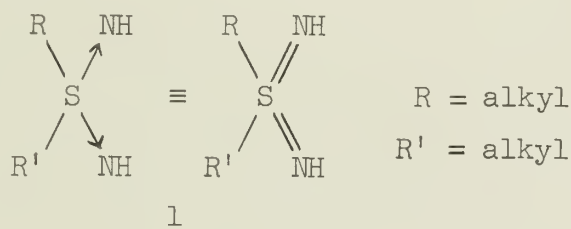
SULFONE DIIMINES

Reported by Lydia E. Moissides

December 19, 1968

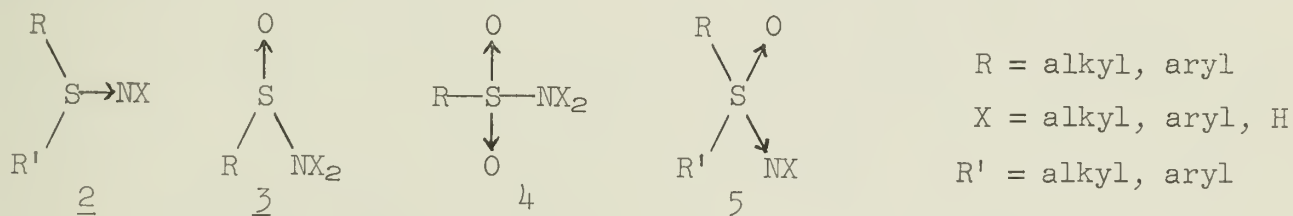
INTRODUCTION

The preparation of imine counterparts of sulfones and studies on their structure and their properties have recently been actively undertaken following the isolation of the adduct from the reaction of a dialkyl sulfide with chloramine reported by Cogliano and Braude in 1964.¹ These authors assigned a hydrazine-type monomeric-dimeric structure to this species. Appel and his coworkers,² on extending the study of chloramination of thioethers, proposed that the structure of the adduct reported by Cogliano and Braude was sulfone-like, with the two oxygen termini replaced by imino groups; in 1967 Laughlin and Yellin³ presented spectroscopic and chemical evidence which supported the structure assigned by Appel in 1966. An X-ray study of dimethyl sulfone diimine by Webb and Gloss⁴ served as further confirmation of the sulfone-like structure. With the synthesis of dialkyl sulfone diimines 1, all possible types of sulfone- and sulfoxide-type imines have now been synthesized and studied. Therefore, before considering the sulfone diimines, some related types of compounds will be discussed briefly.



NOMENCLATURE

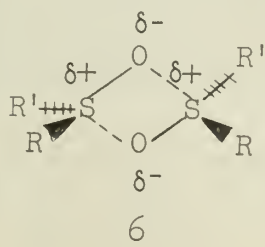
The nomenclature which will be used in this seminar is that suggested by Laughlin and Yellin³ and Appel *et al.*² Compound 1 will be termed a sulfone diimine; 2, a sulfinimine, although sulfilimine also appears in the literature; 3, a sulfinamide; 4, a sulfonamide; and 5, a sulfone imine, whereas sulfoximine is used by Chemical Abstracts and by other authors.



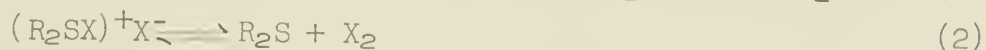
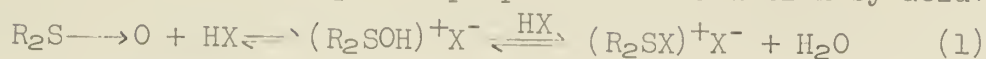
SELECTED ORGANIC SULFUR COMPOUNDS

There has been much published on the structure, preparation, physical and chemical properties, and reactions of the known classes of organic sulfur compounds,⁵ so it is unnecessary to review these in this seminar; but it is helpful to mention briefly the properties of some classes which are related to sulfone diimines.

The chemistry of the sulfoxide grouping permits a comparison of the properties of the S=O (S→O) bond with those of the S=N (S→N) bond. The oxygen terminus of the sulfoxide grouping enters into hydrogen bonding with appropriate solvents,⁶ an observation supported by the ability of even high-molecular-weight sulfoxides to dissolve in hydrogen-containing solvents, *e.g.*, in chloroform but not in carbon tetrachloride. The oxygen is believed to associate with the more positive sulfur end of the polar bond of a second molecule of the sulfoxide, 6, as evidenced by the decrease in S-O stretching frequencies with an increase in the extent of close packing of the sulfoxide.⁶ Participation of the sulfoxide grouping as a base in acid-base reactions occurs through the ability of the terminal oxygen to be protonated and to accept vacant orbitals of transition metals to form salts and/or complexes. As the sulfoxide group is an electron-withdrawing group, hydrogens α to it are fairly labile. Reduction and oxidation are both readily accomplished,^{5a,6} the former leading to the corresponding sulfide. Equations (1)



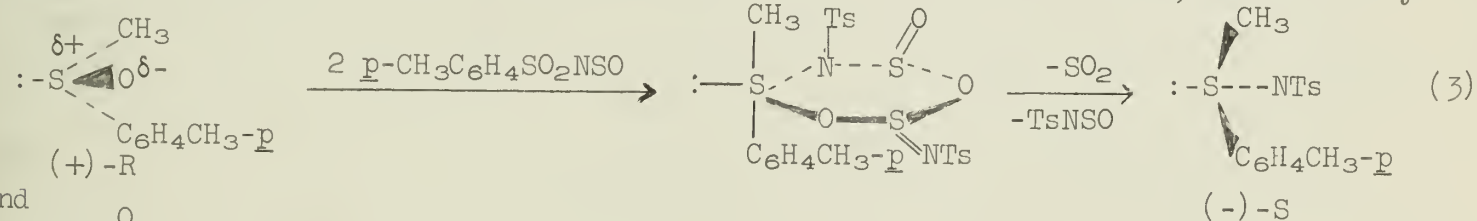
and (2) give the formal reaction sequence proposed for reduction by acid. A detailed



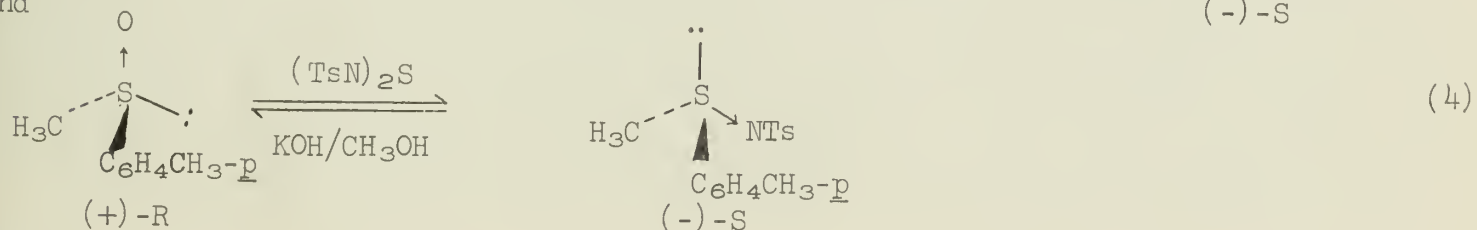
mechanism for the reduction of sulfoxides with hydrogen iodide is given by Landini and coworkers.⁷ Reducing agents used vary from zinc in acetic acid and lithium aluminum hydride to butyllithium. Oxidation with peracids, permanganate, nitric acid, ozone, hypochlorite, halogens, peroxides, etc., leads to the corresponding sulfones.

The temperature sensitivity of sulfoxides depends to a great extent on the bulk of the alkyl groups on the sulfur, but generally speaking sulfoxides are relatively unstable; optically active sulfoxides have been thermally racemized.^{8,9}

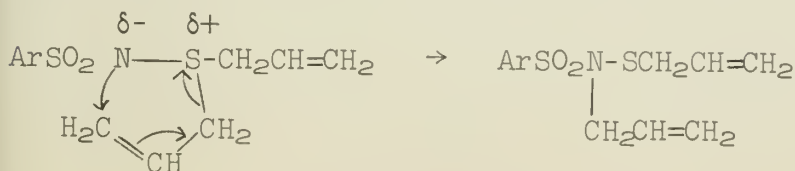
Sulfines are sulfoxide counterparts in which the S-O bond has been replaced by the S-N bond. Their properties are remarkably similar in that the S-N linkage (a) can be cleaved by acids through the N-protonated form,¹⁰⁻¹⁵ (b) is resistant to basic hydrolysis provided the substituents on the sulfur atom are bulky alkyl groups^{13,16} and not unsaturated,^{*,17} (c) can be readily reduced to the parent sulfides with tin and hydrochloric acid, and hydrogen over palladium,^{10,17} and (d) can be oxidized by peroxide to the sulfones,¹⁷ and by neutral or alkaline permanganate and by perbenzoic acid to the sulfone imine with retention of the configuration at sulfur.^{18,19} The sulfines, however, are more basic than the isosteric sulfoxides.^{20,21} Their reduction to the corresponding sulfides, in acidic medium, is believed to proceed via hydrolysis of the sulfine to the sulfoxide, which is then further reduced to the sulfide.¹⁷ Sulfines are generally less stable thermally than the sulfoxides.³ The free sulfines decompose even at room temperature,^{16,21} while sulfoxides remain stable up to the vicinity of 150°. In a recent paper, Johnson *et al.*²² reported that alkylation of the nitrogen in N-p-toluenesulfonylsulfines--which are readily accessible from the reaction of alkyl sulfides and chloramine-T--is rather smoothly accomplished by trimethyl- or triethyloxonium fluoroborate. It should be noted here that adducts do not form with chloramine-T if diethyl sulfide is substituted by more than two chlorine atoms. According to Mann and Pope "it appears that the more highly chlorinated diethyl sulfides are too feebly basic to yield quadrivalent sulfur compounds with the acidic toluenesulfonamido group."¹⁵ Appel and his coworkers have prepared free sulfines by deprotonating the sulfinium sulfate--formed from the corresponding dialkyl sulfides, sodium methoxide, and 88% aminosulfonic acid under dry conditions--with ammonia.²¹ Optically active sulfines have been prepared more recently, by Cram and his coworkers, from optically active sulfoxides, with inversion of configuration at sulfur (*e.g.*, equations (3) and (4)).^{14,19} The reactions are highly stereospecific. The N-substituted sulfine, N-aryl-S,S-dimethylsulfine, was recently



and

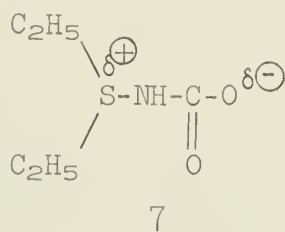


*Sulfines with unsaturated substituents on the sulfur atom undergo spontaneous rearrangement to the N,N,N-trisubstituted species.

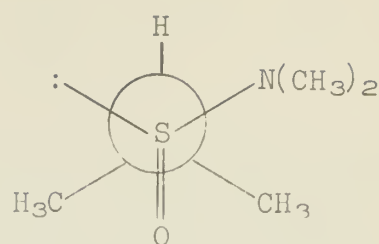
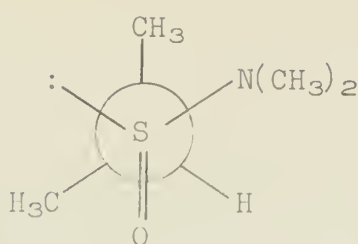
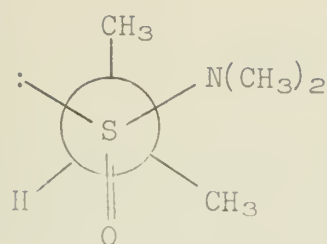


prepared as an intermediate in the reaction of dimethyl sulfoxide (DMSO) with substituted anilines over phosphorus pentoxide during the study of the thio-methoxymethylations of aromatic amines; it was characterized by nmr, ir, and uv spectra.¹³

Verification of the basicity of the sulfimine moiety was given by Appel et al. who reported that N-p-toluenesulfonyldiethylsulfimine can be obtained from diethylsulfimine when it is treated with p-toluenesulfonyl chloride, the carbamic acid derivative 7 can be obtained from the same on treatment with dry carbon dioxide,²¹ and picrates can be formed on addition of picric acid to diethylsulfimine.²



Sulfinamides have the sulfoxide grouping incorporated in them, but one of the alkyl groups has been replaced by a trivalent nitrogen group. They can be obtained from the reaction of oxosulfonium fluoroborates with sodium methoxide in methanol or sodium hydride in DMSO,²³ and from the reaction of alkane sulfinyl chlorides with an N-alkylated reagent;²⁴ they are also prepared stereospecifically in the reaction between a sulfinato ester and lithium anilide.²⁵ Sulfinamides are unstable to acids.²⁶ Their oxidation to the corresponding sulfonamides is effected by hydrogen peroxide or alkaline potassium permanganate.²⁷ Sulfinamides are sufficiently stable to be studied by nmr spectroscopy in deuteriochloroform, carbon disulfide, and benzene. Geminal protons adjacent to the sulfinamido group are magnetically nonequivalent, a situation comparable to that which exists in cases of protons on a carbon atom adjacent to an unsymmetrically-substituted carbon. From a consideration of the nmr spectral patterns of S-alkyl and N-alkyl groups in sulfinamides, Moriarty arrived at the conclusion that "the concept of structure for the sulfinamido group which emerges from these studies requires a pyramidal asymmetric configuration at sulfur, and probably a planar sp² configuration at nitrogen."²⁸ The possibility of a "pyramidal structure [at nitrogen] which is undergoing rapid configuration-inverting vibration" was not excluded, but a locked pyramidal configuration at nitrogen was ruled out owing to the observed equivalence of N-methyl groups (neat or CDCl₃) in N,N-dimethylalkanesulfinamide 8.²⁸ Also, since "even at low temperature" the N-methyl resonances in 8 appear as a sharp singlet in the region δ 2.54-2.87, Moriarty considered improbable the existence of a measurable barrier to rotation about the S-N bond due to d π -p π overlap. He mentioned that he had been informed in a private communication that R. West had demonstrated unhindered rotation about the S-N bond in N,N-dimethylmethanesulfinamide as a consequence of the lack of strict geometric requirements for p π -d π overlap.²⁸ No mention of low-temperature data was made in Moriarty's paper (ref. 28), and no reference to such measurements was given. Proton nmr studies by Jakobsen and Senning²⁹ on N,N-dimethyltrichloromethanesulfinamide in a temperature range of 35° to -80° indicated that at 35° the nmr consisted of a sharp singlet (at τ 7.05) which separated into two peaks, at -46°, that reached their maximum separation of 0.33 ppm at -80°.

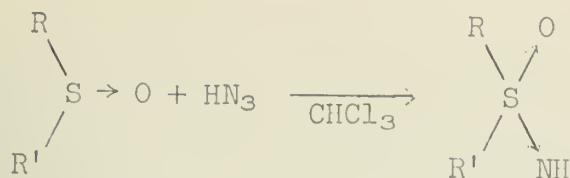


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Unlike the sulfoxides, sulfones are stable toward most oxidizing and reducing agents,^{5a} are thermally stable to 200°,^{5c} and are unaffected by acid or by boiling dilute alkali (sodamide in piperidine is a useful cleavage reagent for sulfones). The acidity of the hydrogens α to the sulfone group can be compared to that of hydrogens α to a carbonyl group.^{5a,5c}

The stability of the S-O linkages in sulfones is found also in sulfonamides which are very stable and difficult to hydrolyze in either acid or base.^{5a,30,31} The resistance of sulfonamides to alkaline hydrolysis is explained by the apparent shielding of the sulfur atom from the nucleophilic hydroxide ion by the more electronegative oxygen and nitrogen atoms. This explanation is also given for the fact that sulfonamides are resistant to anionic reducing agents, although they are susceptible to reduction by hydrogen bromide, hydrogen iodide, and zinc in acetic acid.³² When hydrolysis does occur in strong aqueous acids it is believed to proceed through protonation of the amide nitrogen rather than by protonation of the oxygen atom.^{30,32,33} In nmr studies in fluorosulfuric acid at low temperature where proton exchange is slow, N-methyl signals in N,N-dimethylalkanesulfonamides show further splitting. The existence of two protonated tautomeric forms (O- and N-protonated) or the rapid intramolecular exchange between such forms³⁴ are not excluded on the basis of the nmr data obtained; however, the proportion of O-protonated tautomer is likely to be small since the observed coupling constants between N-CH₃ and N-H protons are comparable in magnitude to those in methylammonium ions where no such tautomerism is possible.³⁵ Laughlin postulated the existence of "significant double bond character" in the S-N linkage on the basis of the following complementary pieces of evidence: a) the greater magnitude of the acidifying effect of the neutral CH₃SO₂-group on a tetrasubstituted nitrogen atom, compared to that of a charged group, which is difficult to explain by purely inductive electron withdrawing effects; and b) the observation that protonation deshields S-methyl groups more than N-methyl groups.³⁰ A similar postulate had earlier been made by Herrick and Wagner³⁶ and Trueblood and Mayer³⁷ on the basis of ir evidence and X-ray data on sulfamide film.

The assignment of the sulfone imine structure to a toxic methionine derivative by Bentley and his coworkers³⁸ in 1950 prompted further investigation on the nature of the group which has one S=O bond and one S-N bond. By far the most common method for sulfone imine preparation is the reaction between the desired parent sulfoxide and hydrazoic acid (prepared in situ from sodium azide and sulfuric acid) in a dry atmosphere.^{11,23,38-40} Other methods of preparation are the oxidation of sulfinines with permanganate or perbenzoic acid,^{16,18,19} the decomposition of sulfonyl azide



R,R' = alkyl, alkyl; alkyl, aryl;
aryl, aryl

in the presence of copper and the sulfoxide precursor of the desired sulfone imine,^{19,41} and hydrolysis of the corresponding N-substituted sulfone imine with concentrated acid.^{11,19,42} Cram and his coworkers¹⁹ have determined that the reactions of an optically active sulfoxide with copper and toluenesulfonyl azide, or an optically active sulfimine with *m*-chloroperbenzoic acid in sodium carbonate very probably proceed with retention of configuration at sulfur since both reactions involve electrophilic attack on the electron pair of the sulfur. The hydrolytic method for the preparation of the unsubstituted sulfone imine also proceeds with retention of configuration at sulfur, as no direct attack on the sulfur is involved in this reaction. The sulfone imine thus obtained is of known configuration, and when reacted with nitromethane and nitrosyl hexafluorophosphate it gives the corresponding optically active sulfoxide with retention of configuration at sulfur. This series of reactions (sulfoxide \rightarrow substituted sulfimine \rightarrow substituted sulfone imine \rightarrow unsubstituted sulfone imine \rightarrow sulfoxide) has synthetic utility because it makes possible the preparation of optically active sulfoxides hitherto inaccessible through platinum resolution methods or Grignard syntheses.¹⁹

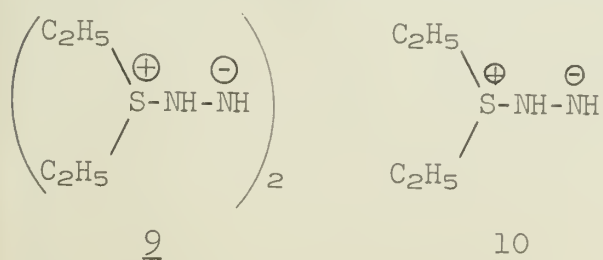
Aromatic sulfone imines are more basic than their aliphatic counterparts,³⁹ and both are more basic than their sulfoxide precursors.¹¹ The sulfone imine group is very stable: it permits the preparation of N-chloro and N-metallo derivatives¹⁹ by electrophilic substitution on the nitrogen, and N-alkyl derivatives by reaction with compounds such as trimethyloxonium fluoroborate and electrophilic olefins,²² and it is quite resistant to hydrolysis. Compounds of this class will, however, undergo decomposition on prolonged reflux in strongly acidic or basic media, and are also subject to thermal decomposition at high temperature.^{11,39} The resistance of the sulfone imine moiety to mild hydrolysis is attributed to the stability of an S-N bond when the sulfur is also linked to an oxygen, a situation similar to that which exists in sulfonamides.¹⁷ With respect to thermal stability, the sulfone imines bear a greater resemblance to the sulfones, which decompose at temperatures higher than 200°, than to the sulfone diimines, which decompose at temperatures of 100° or greater.³ Oxidation of sulfone imines to the corresponding sulfones occurs readily, but their reduction is not as facile as with sulfoxides.¹¹

SULFONE DIIMINES

With the substitution of the second S \rightarrow O bond of sulfones by a S \rightarrow N bond, there arises the class of compounds known as sulfone diimines.

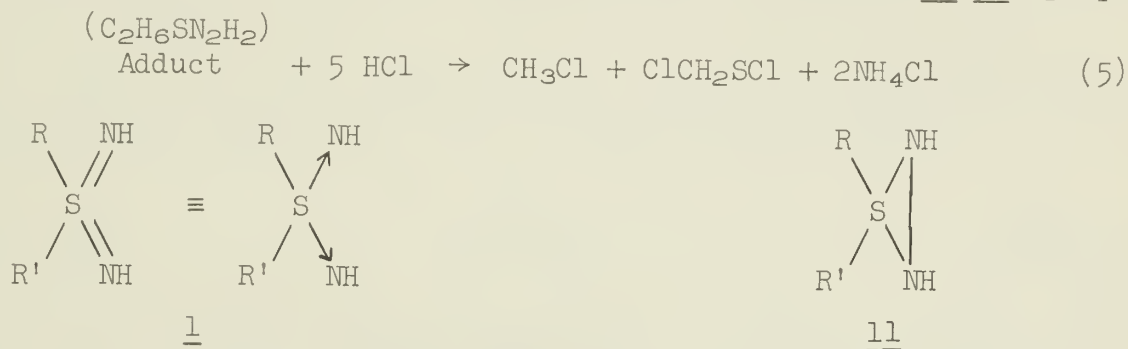
The synthesis of free sulfone diimines is effected by the reaction of alkyl sulfides with chloramine followed by hydrogen chloride cleavage with sodium or potassium carbonate. Although the polarity of the N-Cl bond in chloramine is small, it can be polarized in either of two ways, and this enables chloramine to act either as a chlorinating or an aminating agent.⁴³ The sulfone diimines synthesized to date (dimethyl-, diethyl-, methyl decyl-, methyl dodecyl-, and methyl tetradecyl sulfone diimines) are highly hygroscopic solids at room temperature.

Cogliano and Braude¹ in 1964 isolated a product from the reaction of diethyl sulfide with chloramine to which they assigned structures 9 and 10. They drew



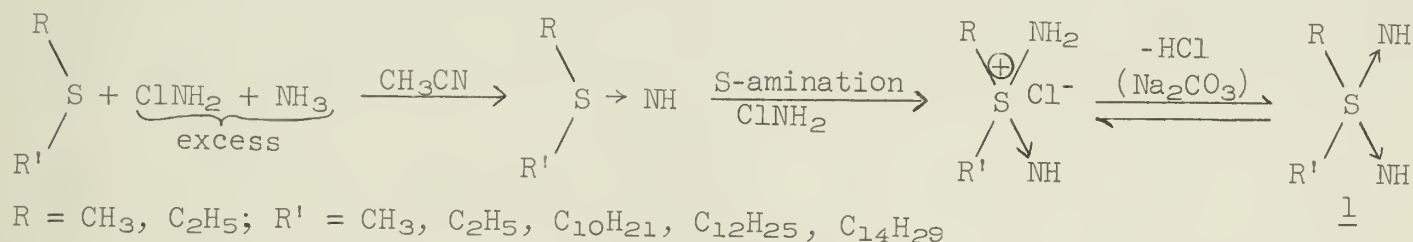
support for these structures from nmr and ir spectra, the ebullioscopic molecular weight determination, and mass spectrometric data. They went so far as to stipulate that in the solid state and in solution the free base exists as a dimer, while in the gas phase it exists as the monomer. The adduct was found to have neither oxidizing nor reducing properties, and to be insoluble in non-polar solvents.

The reaction between dimethyl (and diethyl) sulfide and chloramine was repeated by Appel and his coworkers in 1966,² and the highest yield of adduct was obtained when acetonitrile was used as the solvent; hydroxylic media are avoided in order to minimize the likelihood of hydrolysis of the intermediate sulfimine to the sulfoxide.³ The inertness of the adduct to oxidizing agents such as potassium permanganate, iodic acid, and ammoniacal silver nitrate speaks against structures 9 and 10. Also, since reaction of the adduct, in solution in methylene chloride, with excess hydrochloric acid gives ammonium chloride quantitatively, equation (5), structures 9 and 10 cannot be correct as these would be expected to give either nitrogen or hydrazinium chloride, but not ammonium chloride quantitatively. Hydrolysis products were not detected. To account for the observed chemical properties, Appel et al. proposed



two plausible structures for the sulfone diimine, 1 and 11; 1 is more compatible with the observations and it is the only one supported by the mass spectrometric data: if either the zwitterionic structures or the ring structure were correct, in addition to the different fragments with two nitrogen atoms there would also be found peaks corresponding to N_2H^+ (m/e 29) and N_2H_2^+ (m/e 30). However, only a background peak of less than 2% intensity was found for m/e 29, and accurate mass determination showed that m/e 30 corresponded to the species CH_4N^+ ($\text{CH}_2=\text{NH}_2^+$) rather than N_2H_2^+ (calcd. for CH_4N^+ 30.0344, for N_2H_2^+ 30.0218; found 30.0342 \pm 0.0002). The base peak at m/e 77 was attributed to $[\text{CH}_3\text{S}(\text{NH})_2]^+$, an assignment made by analogy to the pattern found for the corresponding sulfone (m/e 79 for CH_3SO_2^+) and the sulfone imine (m/e 78 for CH_3SONH^+).²

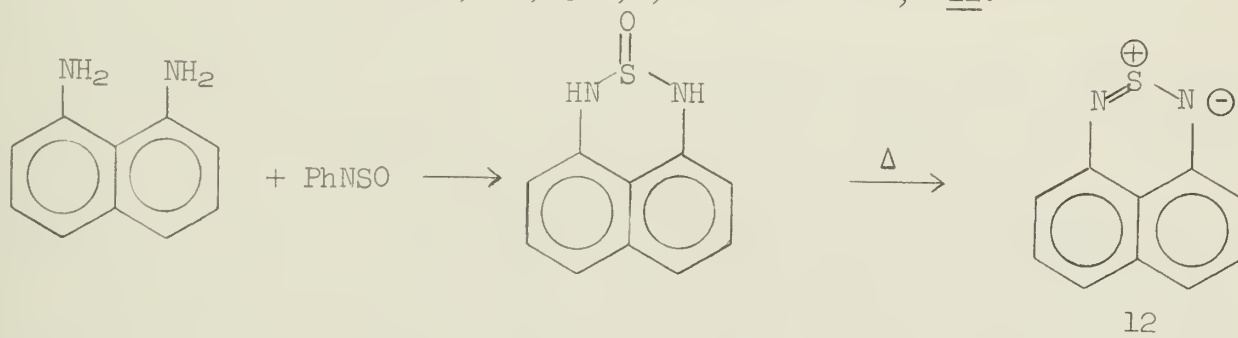
In 1967, Laughlin and Yellin³ proposed the following scheme for the reaction



of dialkyl sulfides and chloramine. The thermal and hydrolytic stability of sulfone diimines was found to exceed that of sulfimines, and it is generally found that the sulfone-type imines are more stable, hydrolytically, than sulfoxide-type imines. The reluctance of the sulfone diimine moiety to undergo acid- or base-catalyzed hydrolysis to the sulfone imine or sulfone group constitutes supporting evidence for structure 1. The related sulfone imines are also stable to hydrolysis. On the other hand, the hydrazine-type structures, 9 or 10, being N-substituted sulfimines would be expected to resemble the parent sulfimine by being readily hydrolyzable.

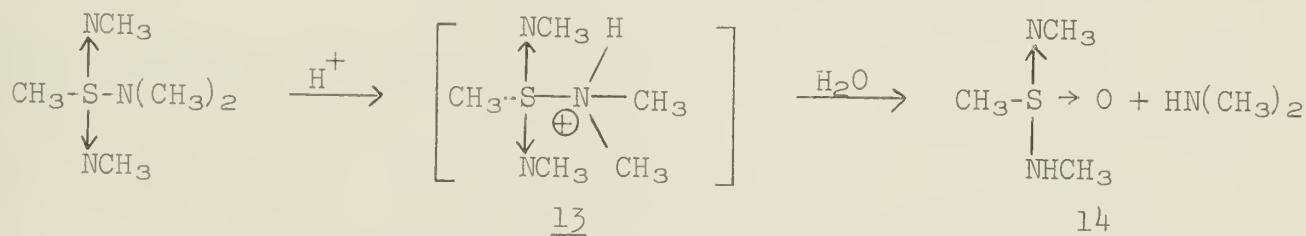
Even though sulfone diimines are less basic than the corresponding sulfimines, a situation analogous to that which exists between sulfones and sulfoxides, the sulfone diimine group is basic enough to complex with vanadium (IV), chromium (III), iron (III), and copper (II).³ Another important property of the sulfone diimine moiety is its polarity, which enables it to enter into hydrogen bonding both in the crystalline state and in solution with polar hydrogen-containing solvents; it does so to a much greater extent than its oxygen counterpart, namely the sulfone group. The extent of hydrogen bonding can be followed spectroscopically; in solvents in which formation of hydrogen bonds is favored, a decrease in N-H stretching frequency and a broadening of the N-H stretching band is observed. In the crystalline state hydrogen-bond formation is even more pronounced.

From X-ray data on dimethyl sulfone diimine, Webb and Gloss⁴ postulated that the S-N bonds in sulfone diimines have appreciable double bond character. The S-N bond distances were found to be essentially those of an S-N double bond as predicted by the Pauling radii;⁴⁴ they are shorter than S-N bonds in compounds with S-NH₃ and S-NH₂ groups, and the explanation given for the decrease in bond length on changing the number of groups on the nitrogen atom is that the increasing availability of p-orbitals on nitrogen as hydrogen atoms are removed increases the π -bond character of the S-N bond.⁴ Also, if any parallel can be drawn between sulfur diimides (-N=S=N-) and sulfone diimines, the S-N bonds of sulfone diimines could be expected to show both double bond and polarizable character; Ulrich in his review of the somewhat limited information on the chemistry of sulfur diimides indicates that sulfur diimides undergo Diels-Alder-type cycloaddition reactions with a variety of double bond systems, in some instances giving six-membered ring heterocycles with the N-S-N group incorporated in the ring; he therefore suggests that "the semipolar character of the bonding in the -N=S=N- grouping apparently allows for the bending necessary for formation of the six-membered ring in naphtho[1,8-c,d]-1,2,6-thiadiazine," 12.^{5d}



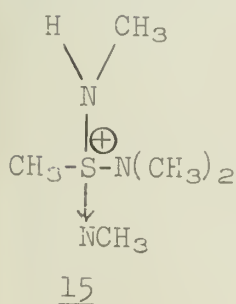
In comparing the properties of sulfoxides and sulfones with their nitrogen analogs, it is found that the latter are less stable thermally than the former; also, the nitrogen-containing compounds are more basic than their oxygen counterparts, and have greater metal-complexing ability.

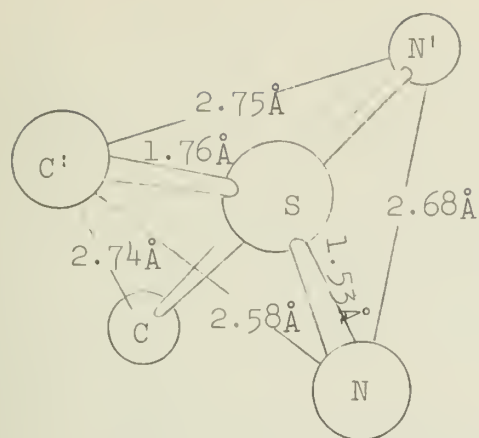
Attempts to prepare the bis(N-methylated)dimethyl sulfone diimine from dimethyl sulfide and methyl chloramine failed;⁴⁵ this reaction, however, yielded the corresponding sulfonamide bis(methylimine) which can be readily and quantitatively hydrolyzed to the sulfonamide methylimine by acid--an observation which stands in contrast to the inertness of sulfone diimines to acid-catalyzed hydrolysis. Investigation of this apparent difference in properties disclosed that protonation occurs on the amide nitrogen, thus selectively cleaving the sulfur-amide bond. Intermediate



13 was favored over 15 because protonation on the imine nitrogen, which would be expected from consideration of basicities, cannot be reconciled with either the inertness of the diimines which are incapable of forming a species like 15, or with the apparent selectivity of this reaction for cleavage of the S-N amide linkage. No explanation for the failure of methylimines, 14, to undergo hydrolysis, even under drastic conditions (100° for 10 hr in 13.9 M sulfuric acid), was proposed. The bis(methylimines) are more basic, by about 2 pK_A units, and thermally much less stable than the methylimines, relationships which parallel those between the sulfone diimines and the sulfone imines. Those bis(methylimines) and methylimines which have amide hydrogens can be readily alkylated on the amide nitrogen in the presence of sodium hydride.⁴⁵

Figure 1 depicts the structure of dimethyl sulfone diimine as determined by Webb and Gloss⁴ by X-ray single crystal techniques (% R = 7.7). A slightly distorted





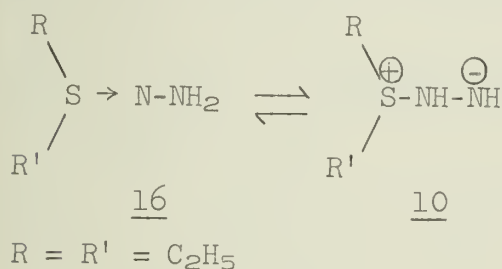
$$\begin{aligned} SC &= SC' = 1.76 \pm 0.05 \text{ \AA} \\ SN &= SN' = 1.53 \pm 0.04 \text{ \AA} \\ \widehat{NSN'} &= 122^\circ \pm 3^\circ \quad \widehat{NSC'} = 103^\circ \pm 2^\circ \\ \widehat{CSC'} &= 103^\circ \pm 3^\circ \quad \widehat{NSC} = 113^\circ \pm 2^\circ \end{aligned}$$

Figure 1. Structure of dimethyl sulfone diimine as determined by X-ray crystallography.

tetrahedral structural assignment was made.

A tetrahedral assignment was also made by Laughlin and Yellin,³ who undertook the structure determination of dialkyl sulfone diimines using mainly Raman spectroscopy; they reasoned that since 1 and 10 have unlike skeletal symmetry, their vibrational spectra ought to make it possible to differentiate between them.

Raman spectra taken on a concentrated aqueous solution of dimethyl sulfone diimine were compared with those of liquid dimethyl sulfide and liquid unsymmetrical dimethylhydrazine. The bands due to the $(CH_3)_2S$ functional group were retained in the dimethyl sulfone diimine spectrum, while the pattern differed from that of the dimethylhydrazine; most noticeable was the absence of a band in the $700\text{--}900\text{ cm}^{-1}$ region, which is the N-N stretching region in hydrazine structures. No bands were found at 1606 cm^{-1} and 3207 cm^{-1} , assigned to the NH_2 scissor (δNH_2) and $2\delta(NH_2)$, respectively, thus eliminating the possibility of a structure like 16. Evidence against 16 was also



found in the fact that only a single band at 3311 cm^{-1} appears in the Raman and ir of a chloroform solution of the dimethyl sulfone diimine indicating the degeneracy of the in-phase and out-of-phase NH stretch in the molecule (three bands are assigned to the NH stretch in crystalline sulfamide).³⁶ The various vibrational band assignments were made in accord with data reported for sulfamide film (ir), dimethyl sulfone (Raman) and dimethyl sulfide (Raman).^{3,36}

Another comparison which substantiated the tetrahedral assignment was that between the Raman spectrum of solid dimethyl sulfone diimine and that of dimethyl sulfone imine; these had a very similar band pattern, and bands arising from corresponding vibrations were very close in value. Spectral studies were also made with diethyl and methyl dodecyl sulfone diimines. Although the spectral assignments were more difficult to make in these cases, comparison with the spectra of the parent sulfides indicated that the characteristic bands due to the dialkyl sulfide unit remained essentially intact after amination. Vibrational frequency tabulations and a table of characteristic $R_2S(NH)_2$ Raman bands are given in reference 3.

CONCLUSION

The work of Laughlin, Appel, and Webb and their coworkers seems to have established conclusively the tetrahedral structure of dialkyl sulfone diimines, and it has considerably extended the information on the properties of S-N bonds in the sulfone-type imines; nevertheless, it is readily apparent that further work is necessary particularly in the area of preparation and examination of properties of the N-substituted sulfone diimines.

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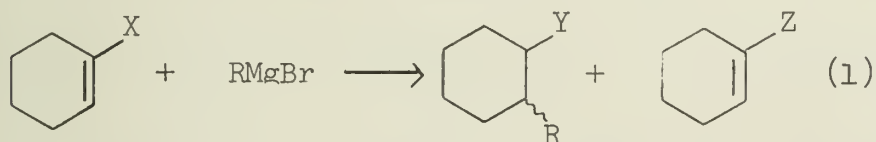
CONJUGATE ADDITIONS OF GRIGNARD REAGENTS TO CARBONYL COMPOUNDS

Reported by Katie Thornburg

January 6, 1969

The synthetic potential of the conjugate addition reactions of Grignard reagents has been recognized for over sixty years. Research conducted prior to 1950 has been summarized by Kharasch and Reinmuth¹ and has uncovered the wide variety of unsaturated carbonyl compounds to which this reaction is applicable. Since that time, systematic investigations have been concerned with mechanistic and stereochemical considerations involved in the conjugate mode of Grignard reagent addition and with those factors which favor conjugate (1,4-; 1,6-; and 1,8-) over normal (1,2-) addition. Reproducible studies designed to elucidate the effect of the reactivity and steric bulk of the carbonyl moiety, the cyclic or ionic character of the transition state, the catalytic role of the cuprous ion, and the degree of stereoselectivity obtainable will be discussed in this seminar.

Factors enhancing 1,4-addition attributable to the functionality in conjugation with the carbon-carbon double bond include increasing steric size and decreasing reactivity toward nucleophilic reagents. Results of a thorough investigation of these factors conducted on the relatively rigid 1-cyclohexenyl system according to the reaction (1) are summarized in Table I.²

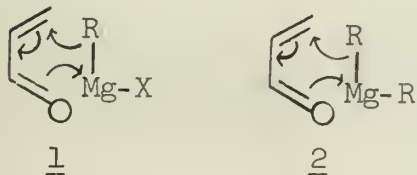


Methyl trans-2-phenylcyclohexanecarboxylate and cis- and trans-2-phenylcyclohexanecarboxylic acid react only slowly with phenylmagnesium bromide, affording

60 and 90% recoveries of starting materials under conditions which lead with their cyclohexenyl counterparts to 56 and 67% yields of products. The ketonic products of phenylmagnesium bromide addition to the unsaturated ester and acid thus result from the initial formation of 1-cyclohexenylphenone which then undergoes attack in a conjugate manner. This is consistent with an expected low reactivity toward nucleophiles of the enolate formed via 1,4-addition.

Although both steric and electronic factors contribute to the reactivity of the carbonyl toward Grignard reagents, steric factors appear to predominate in determining the ratio of normal to conjugate addition. Significant amounts of 1,4-addition are observed in the reactions between phenylmagnesium bromide and 1-cyclohexenylphenone, -dimethylamide, and -carboxylic acid. The corresponding methyl ketone and unsubstituted amide respond predominantly to 1,2-attack. In comparing the two ketones, however, it may be argued that the benzoyl function inductively enhances conjugate reactivity. With a less sterically demanding Grignard reagent (benzylmagnesium chloride), 1,2-addition is favored even for the relatively inert acid. Similar steric effects have been observed in the course of Grignard reagent reactions with α,β -unsaturated esters of branched chain alcohols relative to their straight chain analogs.^{3,4} Similar electronic effects have been noted in the propensity of cinnamic and crotonic acids to undergo 1,4-addition which is not shared by their simple aliphatic esters.⁵














The cyclic six membered transition state originally formulated as 1 by Lutz and Reveley⁶ and alternatively designated as 2 (corresponding to different authors' then contemporary views concerning the structure of the Grignard reagent) has been invoked to account for variations in the yield of conjugate addition product obtained from geometrically isomeric enones and enesters, and to explain the preferential 1,4-addition of Grignard reagents to systems in which electronically favored 1,6-addition is possible.



In Table II are compiled the experimental results of various investigations designed to corroborate the cyclic nature of the transition state for 1,4-addition. These experiments were conceived on the basis of a hypothesis requiring further clarification: if a cyclic mechanism is operative a compound with a substituent cis to the conjugated carbonyl should lead to a smaller amount of 1,4-addition product than the corresponding trans isomer under identical reaction conditions. As presented, this argument neglects any possible effect of geometrical isomerism on the transition state for 1,2-addition. Obviously, if steric hindrance introduced by a cis substituent is considered to have an energetically elevating effect on the transition states for both 1,2- and 1,4-

Table I

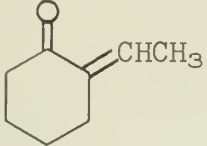
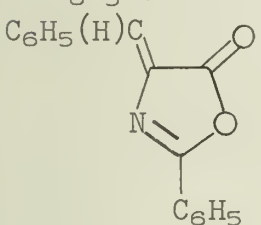
Product Analysis of Grignard Reagent Additions to 1-Cyclohexenyl Systems²

<u>X</u>	<u>R</u>	<u>Y</u>	<u>Z</u>	Relative %'s			Comments
				<u>1,2</u>	<u>1,4</u>	<u>1,2</u> + <u>1,4</u>	
C≡N	C ₆ H ₅	-	COC ₆ H ₅	100	-	-	Product obtained after hydrolysis of the chloroimine; 5 hr reflux in ether; varying molar ratios RMgBr: 
	α-C ₁₀ H ₇	-	COα-C ₁₀ H ₇	100	-	-	
	C ₆ H ₅ CH ₂	-	COCH ₂ C ₆ H ₅	100	-	-	
	CH ₃	-	COCH ₃	100	-	-	
CO ₂ CH ₃	C ₆ H ₅	COC ₆ H ₅	-	-	-	100	5:1 RMgBr:  ; 56%; 4 hr reflux in ether 1:1 RMgBr:  ; 4 hr reflux in ether
	C ₆ H ₅	COC ₆ H ₅	CO ₂ CH ₃	-	-	100	
CO ₂ H	C ₆ H ₅	COC ₆ H ₅	-	-	42	58	3:1 RMgBr:  ; 17 hr reflux in ether; 77% 3:1 RMgBr:  ; 20 hr; 67% 3:1 RMgBr:  ; 20 hr; 35%
		CO ₂ H		83	17	-	
	C ₆ H ₅ CH ₂ (Cl)	CO ₂ H	C(CH ₂ C ₆ H ₅) ₂	83	17	-	
	C ₆ H ₁₁	CO ₂ H	-	-	6	94	
		COC ₆ H ₁₁					
CONH ₂	C ₆ H ₅	-	COC ₆ H ₅	100	-	-	3:1 RMgBr:  ; 4 hr reflux; 15% 9:1 RMgBr:  ; 20 hr reflux; 70%
CON(CH ₃) ₂	C ₆ H ₅	COC ₆ H ₅	-	-	46	54	20 hr reflux in ether-C ₆ H ₆ ; 60%
		CON(CH ₃) ₂					
COCH ₃	CH ₃	-		100	-	-	3:1 RMgBr:  ; 2 hr reflux in ether; 41% %'s by ir analysis
	(w. CuCl)	COCH ₃	"	<1	>99	-	
	C ₆ H ₅	COCH ₃		80	20	-	
COC ₆ H ₅	C ₆ H ₅	COC ₆ H ₅	-	-	100	-	3:1 RMgBr:  ; 4 hr reflux in ether; quantitative

addition, the trans isomer will undergo more 1,4-addition than the cis compound if destabilization of the respective transition states is greater for conjugate than normal addition.

Table II

Conjugate Yields in the Reactions of Grignard Reagents with Geometrical Isomers

Substrate	RMgX	Ref.	% 1,4-addition	
			<u>cis</u>	<u>trans</u>
<u>sec</u> -C ₄ H ₉ O ₂ CCH=CHCO ₂ <u>sec</u> -C ₄ H ₉	<u>n</u> -C ₄ H ₉ MgBr	11	39	19
<u>sec</u> -C ₄ H ₉ O ₂ CC(CH ₃)=CHCO ₂ <u>sec</u> -C ₄ H ₉	<u>n</u> -C ₄ H ₉ MgBr	11	62-70	42-55
	C ₂ H ₅ MgBr	9	37.5	63.7
CH ₃ CH=CHCO ₂ <u>sec</u> -C ₄ H ₉	<u>n</u> -C ₄ H ₉ MgBr	7	40	75
CH ₃ CH=C(CH ₃)CO ₂ <u>sec</u> -C ₄ H ₉	<u>n</u> -C ₄ H ₉ MgBr	7	44 (angelic)	72-76 (tiglic)
C ₆ H ₅ COCH=CHCOC ₆ H ₅	C ₆ H ₅ MgBr	8	35	60-65
	C ₆ H ₅ MgBr	10	-	40
<div> <div> <u>a</u> <u>cis</u>;</div> <div> <u>b</u> <u>trans</u> </div> </div>				

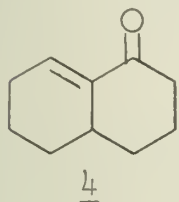
If conjugate addition occurs via a cyclic mechanism, a group cis to the carbonyl may be expected to exert a greater influence on the transition state for this process than on the transition state for normal addition, due to a more direct interaction with the incoming Grignard reagent. Results involving the isomeric crotonic and α -methylcrotonic sec-butyl esters,⁷ dibenzoyl ethanes,⁸ cyclohexylidene ketones,⁹ and azlactones¹⁰ are therefore consistent with the concept of a six membered ring transition state. The enhanced yield of 1,4-addition product obtained from the cis diesters¹¹ may be attributable to a reversal in the relative strengths of the energetic effect of the cis substituent on the two transition states.

Orientation in the conjugate addition reactions of Grignard reagents with $\alpha,\beta,\gamma,\delta$ -unsaturated carbonyl compounds also has been used to provide support for the cyclic mechanism. The conjugate addition products obtained from the reaction of n-butylmagnesium bromide with sec-butyl hexa-2,4-dienoate were partitioned 3:1 between 1,4- and 1,6-adducts.¹² The reaction of ethylmagnesium bromide with hepta-3,5-dien-2-one afforded an equal distribution of 1,2- and 1,4-adducts.¹³ Products resulting from 1,6-addition to this dienone were observed with methylmagnesium iodide and bromide; only in the latter case did the extent of 1,6-addition exceed that of 1,4-addition.¹³ Michael-like additions are known to occur preferentially in a 1,6-fashion with similar substrates.¹² Preference for conjugate addition at the β -carbon implies a stabilization of the transition state for 1,4-addition relative to 1,6-addition. A six membered ring transition state generally is expected to afford more stabilization than an eight membered ring transition state and might be energetically more favorable than addition by a carbanion mechanism.

Although the cyclic mechanism is not excluded by the data thus far presented, its validity as a reaction pathway is also not confirmed. The small differences in yields of conjugate addition product from cis and trans isomers and in 1,6- vs. 1,4-orientation reflect very small energy differences among the transition states under consideration and may be smaller than expected on the basis of a cyclic mechanism. In any event, it may be possible to account for these differences by considering temperature and concentration variations among individual experiments, solvation effects, and other factors. This contention is supported by the fact that Cologne finds no difference

in the relative yields of 1,4- and 1,2-adducts from the addition of ethylmagnesium bromide to either the cis and trans isomers of 3-propyl-3-hexen-2-one or those of 3-hepten-2-one.¹⁴

Incursion of a cyclic six membered transition state for 1,4-addition was severely criticized by Alexander and Coraor¹⁵ and H. O. House.¹⁶ Although 2-cyclohexenone offers an improbable geometry for the proposed transition state 1 or 2, comparable yields of conjugate addition product are obtained on treatment of 2-cyclohexenone, 3-penten-2-one, 3-hexen-2-one, 4-hexen-3-one, and 3-hepten-2-one with isopropyl and tert-butylmagnesium bromides. Only a small decrease in yield for conjugate addition to the cyclic ketone is noted when ethylmagnesium bromide is employed. The geometry of $\Delta^{8,9}$ -octal-1-one 4 forces a cisoid configuration on the conjugated system. If conjugate addition occurs via a cyclic mechanism, enones not thus constrained might possibly afford lower yields of 1,4-adducts, assuming in all cases that additions to the respective carbonyls are energetically equivalent. A 43% yield of 8-phenyl-trans-1-decalone does not reflect a significant conformational advantage in a cisoid system if compared with the 50% yield of 1,4-adduct obtained by the action of phenylmagnesium bromide on trans-3-penten-2-one.



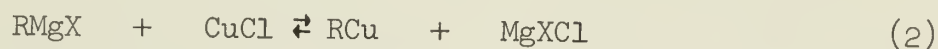
Orientation in the previously mentioned 1,4-additions of n-butylmagnesium bromide to citraconic and mesaconic esters favor the α,α -disubstituted product (9:1 and 7:3, respectively),^{7,11} a result quite surprising in view of the less sterically hindered pathway open to a cyclic transition state for the mesaconic isomer. The results of Munch-Petersen^{7,11} Dubois and Dubois,⁹ Miginiac¹³ and Lutz⁶ which led them to favor a cyclic mechanism are perhaps better noted for their synthetic utility rather than mechanistic significance.

Following Kharasch and Tawney's discovery that cuprous halides are particularly effective catalysts for promoting the 1,4-addition of methylmagnesium bromide to isophorone,¹⁷ investigators have confirmed this effect with other substrates and other Grignard reagents and elaborated on its magnitude. Cuprous ion catalysis is extremely important in enhancing the yield of conjugate addition product under circumstances in which the carbonyl is not sterically inactive toward 1,2-addition and the Grignard reagent is not so large that 1,4-addition is again favored on steric grounds. The yield of conjugate adduct in the reactions of n-butylmagnesium bromide with sec-butyl unsaturated esters^{3,18} and of phenylmagnesium bromide with 1-cyclohexenyl derivatives² and with $\Delta^{8,9}$ -octal-1-one 4¹⁶ is relatively insensitive to cuprous ion catalysis. However, treatment of sec-butyl unsaturated esters with methylmagnesium bromide leads to a useful 1,4-addition only in the presence of cuprous salts.¹⁹ Unsaturated ethyl esters which ordinarily give poor yields of conjugate addition product afford significantly larger amounts of 1,4-adduct in the presence of cuprous chloride.⁴ Cupric acetate,²⁰ cuprous cyanide,²¹ and the copper (I) iodide tri-n-butylphosphine, -phosphite, and trimethylphosphite complexes²² have been found to be catalytically superior to cuprous chloride. This effect has been attributed to an increased solubility of the salt in the reaction medium.

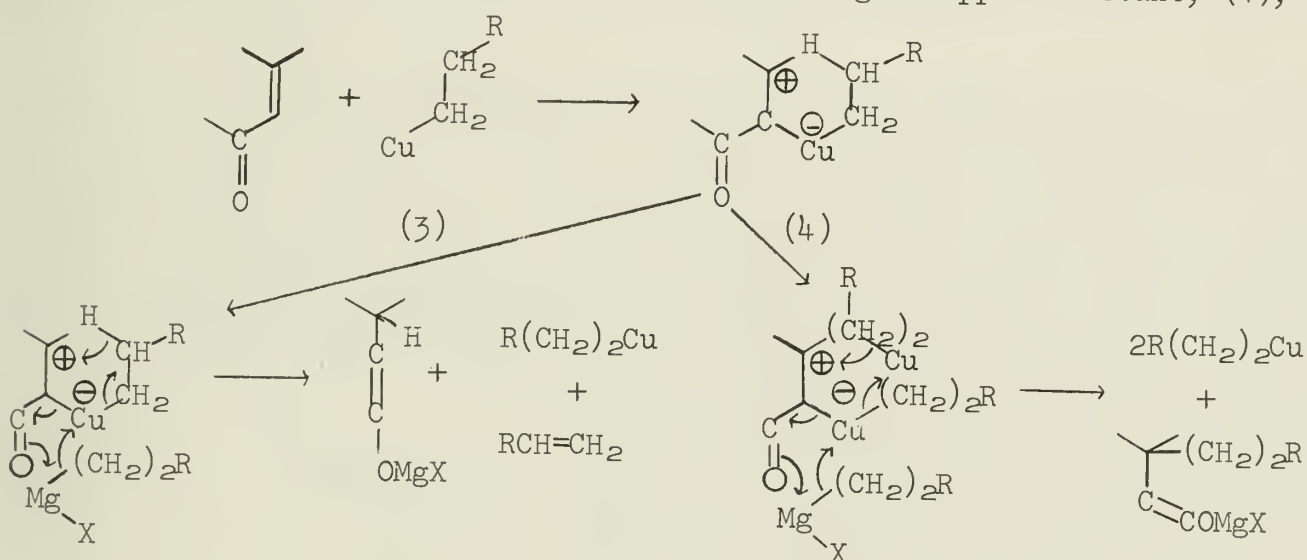
The exact function of the cuprous ion in its catalytic role has been postulated to be either coordinational labilization of the carbon-carbon double bond or formation of a cuprous alkyl (via reaction with the Grignard reagent) which is subsequently more reactive toward the α,β -unsaturated linkage than toward the carbonyl. The former postulate derives support from the known ability of cuprous salts to complex with alkenic linkages,²⁴ the latter from the preparative reaction for synthesizing cuprous alkyls.²⁵ Coordination to the conjugated double bond is viewed by Munch-Petersen as specifically occurring between the α -carbon atom and the cuprous ion, consequently enhancing terminal polarization of the conjugated system.^{11,12} Reaction of the previously cited sorbate ester with n-butylmagnesium bromide in the presence of cuprous chloride affords in 72% yield conjugate addition products consisting of 90% 1,6-adducts and 10% 1,4-adduct.¹² The 1,8-adduct has been obtained in 20-25% yield in the reaction of sec-butyl octa-2,4,6-trienoate under catalytic conditions; no conjugate adduct has been found in the absence of cuprous ion.²⁶ An increased terminal polarization can account for this apparent reversal in orientation of conjugate addition. Although the presence of cuprous chloride enhances the yield of conjugate adduct from the reaction of n-butylmagnesium bromide with the isomeric sec-butyl crotonic esters by 10-15%, the corresponding yield from the α -methylcrotonic sec-butyl ester isomers is decreased

by 7-10%.⁷ This somewhat anomalous result has been attributed to steric crowding in the copper-alkene complex which both slows its rate of formation and sterically inhibits conjugate reaction occurring via a cyclic or carbanion mechanism. The presence of cuprous chloride in the reaction medium increases conjugate addition yields in the reaction of *n*-butylmagnesium bromide with maleic and fumaric *sec*-butyl esters, but decreases this yield with *sec*-butyl citraconate and mesaconate substrates by 30 and 20%.¹¹ In the latter two cases, reduction of the carbon-carbon double bond is the predominant reaction. If coordination of the cuprous ion with the α,β -unsaturated linkage creates a steric problem for conjugate addition, a less spatially demanding reaction such as reduction could indeed be favored.

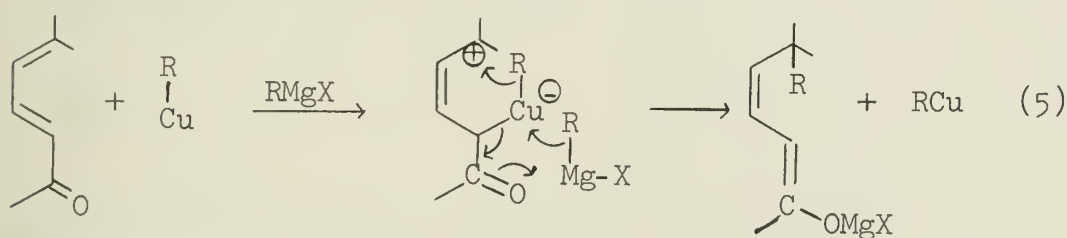
Since reduction cannot take place by a cyclic mechanism, felt by Munch-Petersen to be essential to Grignard reagent reactions, an initial equilibration involving an organocopper species has been proposed (equation (2))¹¹



and this reagent presumably complexes with the α -carbon to afford either (3), reduction, or, with the aid of a second equivalent of organocopper reactant, (4), addition.



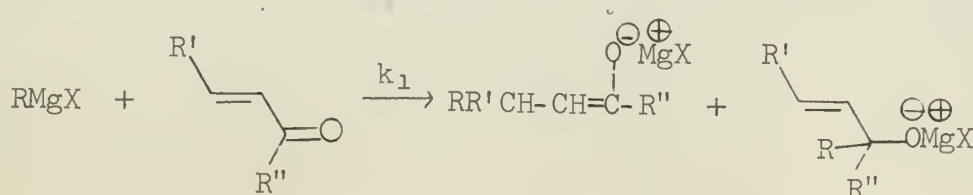
1,6-Addition has been viewed in terms of a cyclic six membered addition (equation (5)) requiring only one equivalent of organocopper reagent:¹²



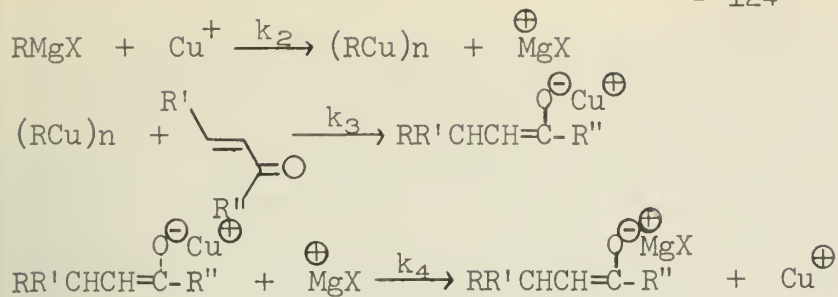
In all cases the organocopper reagent is regenerated during the course of addition. In the presence of a 2:3 molar ratio of cuprous chloride: Grignard reagent, azlactone 3a

reacts with phenylmagnesium bromide to afford the 1,4-adduct in 65% isolated yield and the 1,2-adduct in 2% yield. Two molar equivalents of phenylcopper, prepared from phenylmagnesium bromide and cuprous chloride, and one equivalent of phenylmagnesium bromide react with one equivalent of 3a to give an identical product distribution. Although no other molar ratios of catalyst or organocopper reagent and Grignard reagent have been employed, the authors feel that the identity of the product ratios argue strongly for Munch-Petersen's 1,4-addition mechanism (4).¹⁰

As an outgrowth of an extensive investigation of the reactions of *trans*-3-penten-2-one with Grignard and Grignard-like reagents, House has proposed the following set of equilibria to account for the catalytic effect of copper (I) on conjugate additions:²²



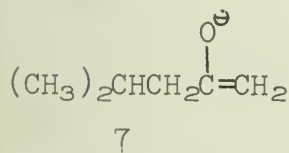
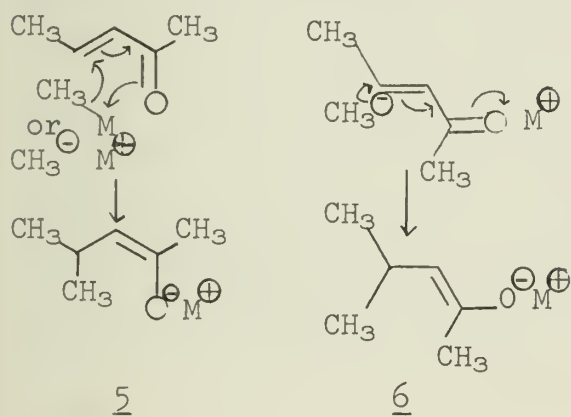
in which k_2 , k_3 , k_4 are all very much larger than k_1 if the organocopper



species is to be competitive with the Grignard reagent. The suggested equilibria are consistent with the over all accelerated rate of addition to the conjugated substrate and with the enhanced yield of conjugate addition product thereby obtained. To lend credibility to the proposed preference of an organocopper reactant

for the conjugate mode of addition, ether insoluble methylcopper (I) and ether soluble lithium dimethylcopper and tri-*n*-butylphosphine methylcopper (I) have been prepared and allowed to react with conjugated and saturated substrates. All three reagents react with trans-3-penten-2-one to yield only the conjugate adduct. The ketone resulting from this addition, 4-methylpentan-2-one fails to react with either the phosphine complex or an ethereal suspension of methylcopper. With lithium dimethylcopper the alkoxide resulting from 1,2-addition is formed to the extent of 31% after two minutes of reaction, whereas in the presence of excess methyl lithium, the reaction attains completion in less than one minute. It has been determined that the organocopper alkylating agent must be complexed with at least one negative ligand to be effective in promoting conjugate addition.²³

To settle the ever present argument concerning the cyclic or ionic nature of the transition state, House has trapped the enolates formed from interaction of the organometallic and trans-3-penten-2-one.²² The cyclic transition state, requiring a cisoid conformation of the conjugated system, leads to the cis-enolate 5, whereas a mixture of 5 and the trans-enolate 6 is to be expected if addition occurs via a carbanion mechanism. This argument assumes that equilibration of the enolates does not occur; i.e., that the enolate retains its stereochemistry of formation. It is known that lithium enolates do not equilibrate in the absence of a proton source such as unreacted ketone.²⁷ Excess Grignard reagent has been used in these experiments. In addition,

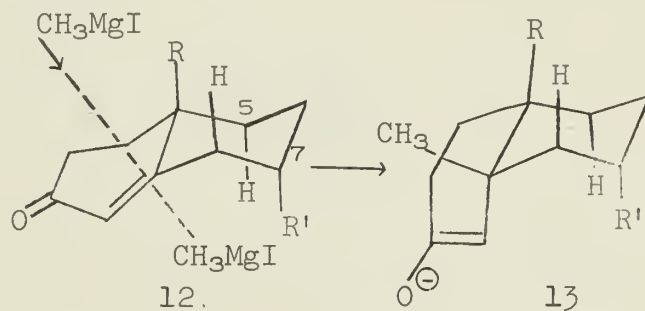


of a 1:1 mixture of cis and trans enolates in the reaction of 1-benzoylcyclohexane and phenylmagnesium bromide in the presence of cuprous chloride.²⁸ To the extent that it may be believed that no equilibration of enolates is occurring, these results demonstrate that at least part of the conjugate addition does not proceed via a cyclic transition state. Although initial coordination of the organocopper species has not been excluded by this study, no chemical or spectroscopic support has yet been uncovered. House consequently has suggested the intermediacy of a charge transfer complex or an electron transfer-radical transfer pathway, but has found no convincing evidence for this route.^{22, 23}

Stereoelectronic and steric factors interact in controlling the stereospecificity of the conjugate addition reaction, and their relative importance can best be assessed if rigid substrates are employed. In the octalonic systems in which organometallic attack occurs at the ring junction, electronic overlap in the π -system can be preserved whether attack proceeds from the top or bottom side of the molecule. Such systems are useful in illustrating the directive effect of steric factors on the conjugate addition reaction. Birch and Robinson have established that the copper catalyzed addition of methylmagnesium iodide to $\Delta^{1,9}$ -octal-2-one 8 affords almost exclusively the conjugate addition product having a cis ring fusion 6 (60-80% yield).²⁹ Subsequently it has been determined that methylmagnesium iodide adds to 10-methyl- $\Delta^{1,9}$ -octal-2-one 9

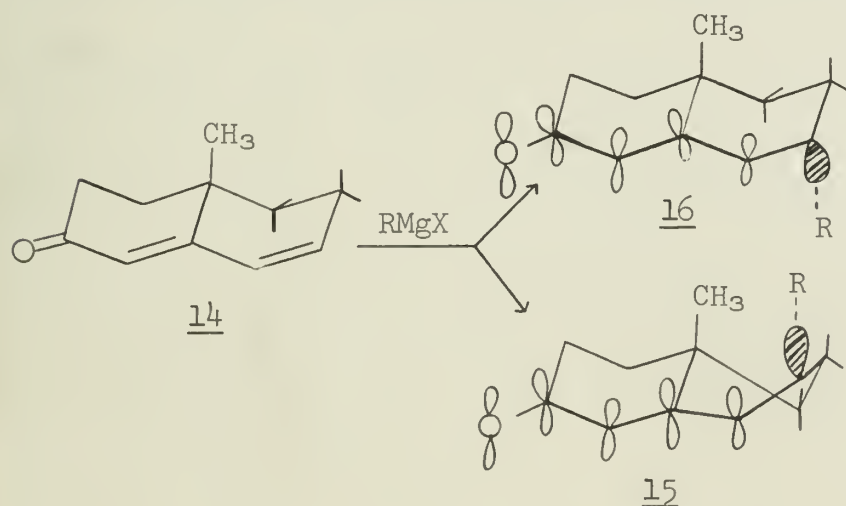
in the presence of cupric acetate to yield the cis fused product (40%).³⁰ Bottom side attack is considerably more sterically hindered by C-5 and C-7 substituents than is top side attack by C-8 and C-10 substituents. Steric hindrance to top side attack presented by the methyl group is reflected in the lowered yield of conjugate addition product. Under identical conditions, and with lithium dimethylcopper,³¹ however, octalones 10 and 11 fail to afford any product of conjugate addition. The octalone epimeric to 11 at C-7 readily undergoes 1,4-addition with lithium dimethylcopper and cupric acetate-methylmagnesium iodide.³¹ Marshall consequently has suggested that the transition state for the conjugate addition reaction resembles the enolate 13, in which steric repulsion between C-4 and the isopropyl or isopropylidene substituent at C-7 is severe.³⁰ Some support for this supposition has been provided by Allinger and Riew,³² who have been able to predict successfully the stereochemical outcome of the cuprous chloride catalyzed conjugate addition of methylmagnesium iodide to 5-

- 8 R = H, R' = H
9 R = CH₃, R' = H
10 R = CH₃, R' = C=CH₂
11 R = CH₃, R' = CH(CH₃)₂



methylcyclohex-2-enone from a consideration of the relative stabilities of the enolates which are formed by top and bottom side attack from the equilibrating cyclohexenone conformers. Reaction of 5-methylcyclohex-2-enone with methylcopper, with equimolar amounts of dimethylmagnesium and methylcopper, and with dimethylmagnesium afford 1-2%, 5%, and 7-10% of the cis dimethylcyclohexanone, thus implicating both reagents in controlling the observed product stereochemistry.²³

Bottom side attack of the organometallic reagent on C-7 of 10-methyl-1(9), 7-hexal-2-one 14 is favored on both steric and stereoelectronic grounds.³³ Maintenance of π -orbital overlap leading to an equatorial introduction of the alkyl group requires the B ring to adopt a highly eclipsed conformation 15 whereas axial introduction allows the reaction to proceed via the more stable conformation 16. The increasing steric requirement of methyl-, ethyl-, isopropyl-, and tert-butylmagnesium halides is reflected in the ratio of copper catalyzed conjugate addition products resulting from 16 to those from 15 which are 93:7, 98:2, 100:0, and 100:0, respectively.

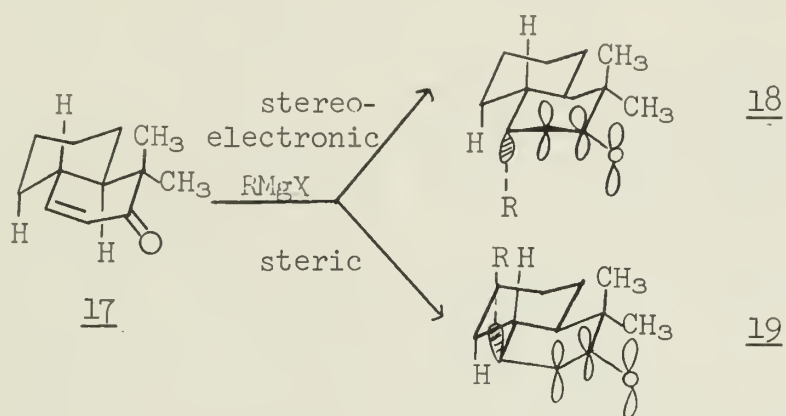


The predominant axial alkylation is also characteristic of analogous steroidal systems.³⁴

Conjugate additions to 1,1-dimethyl-trans-3-octal-2-one 17 provide an opportunity to assess the relative significance of steric and stereoelectronic control to the reaction pathway.³⁵ Top side attack is favored sterically, but in order to maintain π -orbital overlap, ring A must adopt a boat-

like conformation. So long as steric interactions are small, axial introductions, and thus stereoelectronic considerations predominate. In the copper catalyzed addition of methylmagnesium iodide to 17, a 5:1 ratio of axial to equatorial C-4 methyl substituent is found in the conjugate addition product. Phenylmagnesium bromide, in the presence of cuprous ion, affords with 17 almost exclusively the product of bottom

side attack, whereas use of the isopropyl reagent results in nearly equivalent amounts of addition via 18 and 19. However, although the reaction affords only 10% of conjugate addition products, methylmagnesium iodide gives an equal distribution of axial and equatorial adducts in its uncatalyzed conjugate addition to 17.



More striking are the differences in stereochemical outcome between the catalyzed and uncatalyzed conjugate additions of Grignard reagents to the crotonic esters of optically active alcohols. Inouye and Walborsky noted that the uncatalyzed addition of phenylmagnesium bromide to (-)-menthyl crotonate results in a 5.4-6.7% optical yield of S-(+)-3-phenylbutyric acid after saponification of the crude product. When the reaction is run in the presence of a catalytic amount of cuprous chloride, a 5.9-10.2% optical yield of the R-(-)-acid is obtained.³⁶ Kawana and Emoto report a similar instance of differing senses of asymmetric induction involving the 1,2-O-isopropylidene-5-deoxy-D-xylose 20 ester of crotonic acid and the phenyl Grignard reagent.³⁷ The uncatalyzed conjugate addition affords S-(+)-3-phenylbutyric acid in 16% optical yield following saponification, and the catalyzed reaction results in a 58% yield of the R-(-) isomer. In the presence and absence of cuprous chloride, the 1,2:5,6-di-O-cyclohexylidene-D-glucose 21 and 1,2:5,6-di-O-isopropylidene-D-glucose 22 esters of crotonic acid react with phenylmagnesium bromide to give the corresponding R-(-)-acids. The differences in stereochemical outcome have been rationalized on the basis of preferential attack of the organomagnesium reagent and of preferential complexation of the organocopper species at the less hindered side of the carbon-carbon double bond. The organocopper complex presumably undergoes a back side displacement to give a product opposite in configuration at the β -carbon to the one otherwise obtained. The identity of stereochemical outcome in the other asymmetric inductions cited has been attributed to stabilization of an organocopper complex on the more crowded side of the molecule by additional coordination with a sugar oxygen and to preferential carbanion attack instead of complexation. Complex formation on the less hindered side of the molecule followed by back side displacement is inconsistent with the previously cited stereochemical investigations.²⁹⁻³⁵ It is also difficult to accept a mechanistic rationale which arbitrarily invokes complexation and free carbanion attack with little justification beyond an accommodation of the experimental results obtained. It is clear that the mechanistic pathway of catalyzed conjugate addition has not been fully elucidated.

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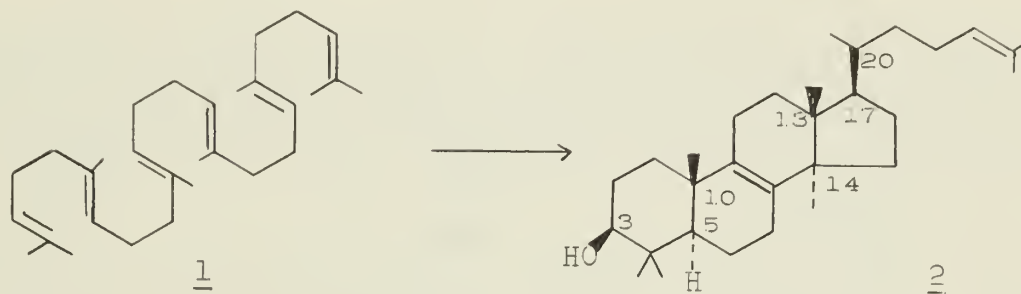
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NONENZYMIC OLEFINIC CYCLIZATION

Reported by Judy P. Chen

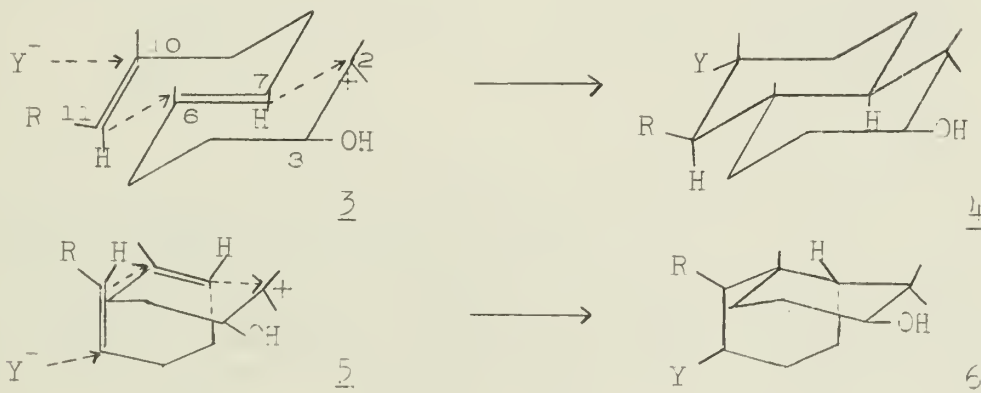
January 9, 1969

It has been unequivocally established¹ that the biosynthesis of lanosterol and, in turn, of cholesterol from mevalonic acid involves an intermediary open-chain polyolefin, namely squalene (1), which undergoes polycyclization and rearrangement to the tetracyclic lanosterol (2). Of particular interest is the fact that squalene (1) which has no center of asymmetry, is converted into a single product with sever



asymmetric centers (at C-3, -5, -10, -13, -14, -17 and -20). This is a truly impressive example of a completely stereoselective process considering there is a theoretical potential of 128 different stereochemical isomers for lanosterol (2).

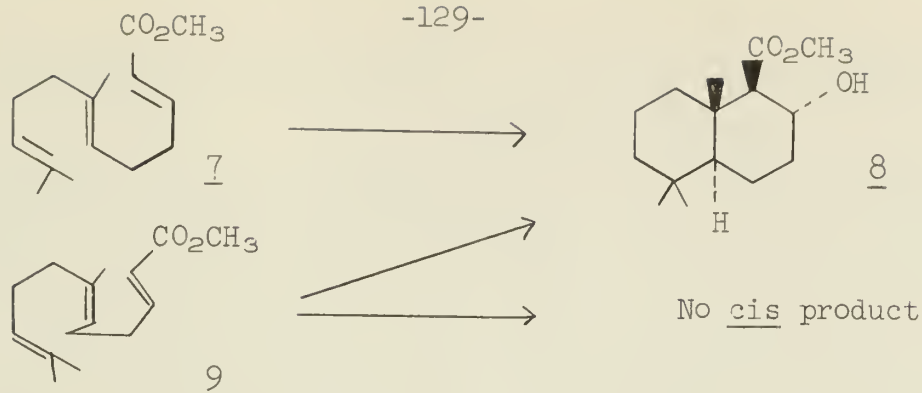
When the biosynthetic role of squalene was recognized, chemists tried to ascertain if squalene or related olefinic systems could be induced to undergo stereoselective cyclization in the absence of enzyme. In 1955 both Stork² and Eschenmoser³ proposed that squalene-like (all-trans) polyolefins should have an intrinsic susceptibility to cyclize stereoselectively to give a product having "natural" configuration. The idea is illustrated below.



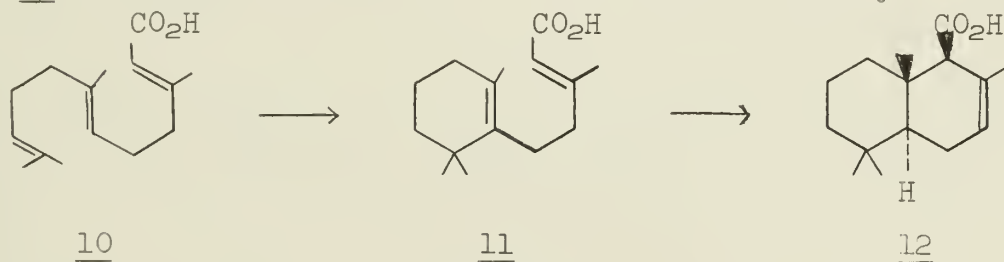
Consider formula 3 which depicts a carbonium ion resulting from protonation of squalene 2,3-oxide followed by opening of the epoxide ring. In essence, the Stork-Eschenmoser hypothesis states that electrophilic attack on the 6,7-olefinic bond by the developing carbonium ion center (at C-2) will be accompanied by a nucleophilic attack by the 10, 11 olefinic bond in such a way that the addition to the 6, 7 olefinic bond is trans. If the 6, 7 olefinic bond has trans geometry, then the rings of the product 4 will be trans fused; otherwise, as in formula 5, the rings of the cyclization product 6 will be cis fused. If the nucleophile Y is an external species, the cyclization process is interrupted with the formation of only two rings; on the other hand, if Y represents an appropriately juxtaposed olefinic bond in the side chain R, the cyclization process may continue further.

ACID CATALYZED CYCLIZATION OF OPEN CHAIN POLYOLEFINS

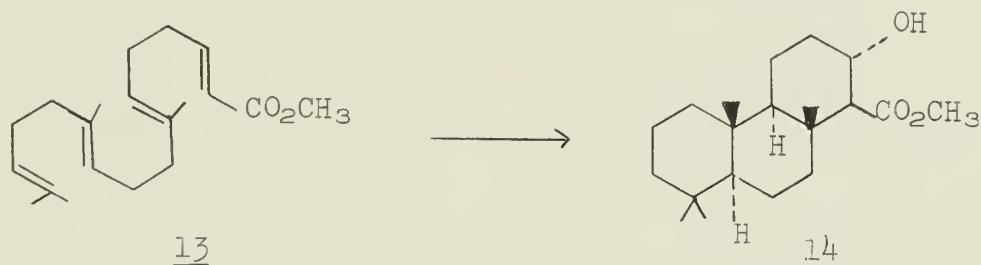
In applying a chemical test of the hypothesis, Eschenmoser and the group at the E.T.H. in Zürich⁴ carried out the acid catalyzed cyclization of ester 7, which yielded a single trans fused decalin derivative (8) in 60-70% yield. However, the same product was produced when the cis substrate 9 was submitted to these cyclization conditions.



Boron trifluoride catalyzed cyclization of farnesic acid (10)² proceeded via an isolable intermediary monocyclic diene 11 which was converted into the bicyclic acid 12 with longer reaction time.⁵ This result suggests that a monocyclic diene similar to 11 was involved as a common intermediate in the cyclization of 7 and 9.



Acid-catalyzed cyclization of the methyl ester 13⁶ gave a crystalline tricyclic hydroxy ester 14 in 5-10% yield. With this low yield, Eschenmoser⁶ concluded that with



polyenes of this complexity, acid-catalyzed cyclization ceased to be a useful reaction from the preparative point of view.

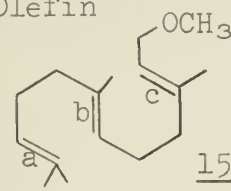
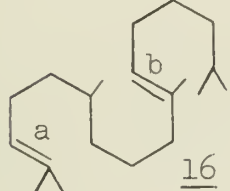
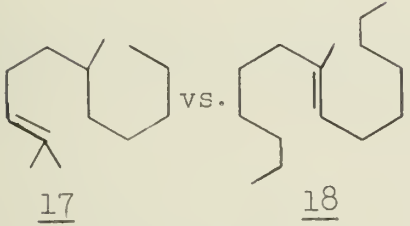
Much of the difficulty encountered in the acid-catalyzed cyclization involves treatment of polyolefinic systems with acid which causes the indiscriminate generation of cationic centers, resulting in competing reactions to give a variety of products. Accordingly, a search was begun for a polyolefinic substrate containing an appropriately positioned functional group that could be used to generate a cyclizable cationic center under conditions which would not otherwise affect the olefinic bonds.

CYCLIZATION OF POLYOLEFINIC EPOXIDES

With the demonstration that squalene 2,3-oxide was converted enzymatically in good yield to lanosterol and cholesterol,^{7,8} the study of terpene terminal epoxides gained added interest and importance. Since squalene and most acyclic terpenes possess only nonconjugated, trisubstituted double bonds which are chemically and sterically equivalent, the selective oxidation of the terminal olefinic link represents a difficult problem. As a means of investigating the selectivity phenomenon, three principal variables were investigated: the structure of the olefinic substrate, the nature of the medium, and the type of oxidizing agent.^{9,10} Some of the results, summarized in Table I, suggest that the *in vitro* selectivity is due to both steric and conformational characteristics of the olefinic system.

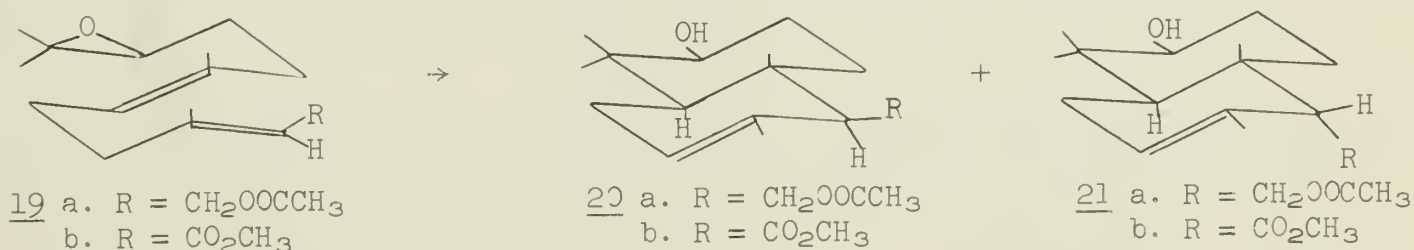
As can be seen from the results with the *trans,trans*-farnesyl methyl ether 15 that the selectivity of epoxide formation is very high, 95% terminal (a) in glyme-water. The same order of selectivity is observed in a purely synthetic example 16

Table I. Selectivity in the Conversion of Olefins to Bromohydrin by NBS

Olefin	Attack Percentages	
	Glyme-water	Petrol. ether-acetic acid
 15	95(a):5(b):(0)	81(a):19(b):0(c)
 16	98.5(a):1.5(b)	62(a):38(b)
 17 vs. 18	100(17):0(18)	

where the double bonds are more widely separated. Similarly, in a competition case involving two long chain olefins, one (17) with a "terminal" double bond and the other (18) with an "internal" olefinic link, the former is oxidized to the virtual exclusion of the latter. A pronounced solvent effect is also shown. In petroleum ether-acetic acid, selectivity in the case of 15 drops from 95% to 81%, and in the case of 16 the change is even more marked, from 98.5% to 62%. A possible explanation of the solvent effect concerns the conformations of the olefins in solution. It has been suggested^{9,11} that in certain solvents coiling of the polyolefin may be more pronounced and therefore more effective in shielding the internal double bonds from oxidative attack and yet permit exposure of the terminal position for reaction. Solvent-clustering around reactive sites of the reagent and olefinic molecule may, by simple bulk effects, discourage reaction at the sterically encumbered central portion of the system. In keeping with this explanation is the low selectivity exhibited by various "neutral" oxidizing reagents, e.g., diimide or osmium tetroxide, as contrasted with the higher selectivity of charged (and therefore more extensively solvated) reagents, such as N-bromosuccinimide and mercuric acetate.

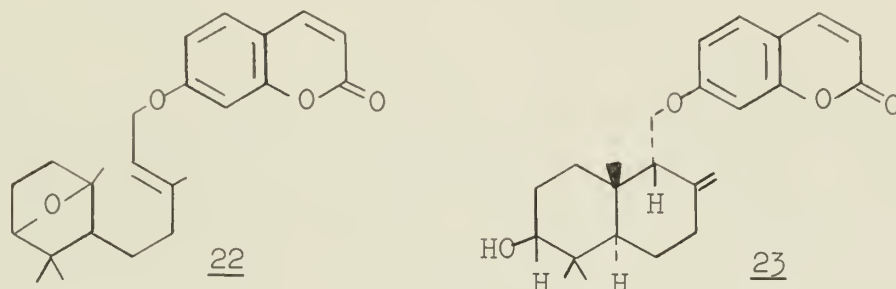
With the solution to the practical problem of selective oxidation within reach, conversion of acyclic terpene derivatives to cyclic systems featuring the hydroxylated A-ring moiety characteristic of cyclic triterpenoid and steroid classes were studied. Some model reactions, such as the cyclization of geranyl acetate epoxide¹¹ and geraniolene monoxide,¹² were carried out and the desired alcohols were obtained. From these two examples it was impossible to determine the stereochemistry of the cyclization, so attention was turned to trans,trans-farnesyl acetate terminal epoxide (19a).¹³



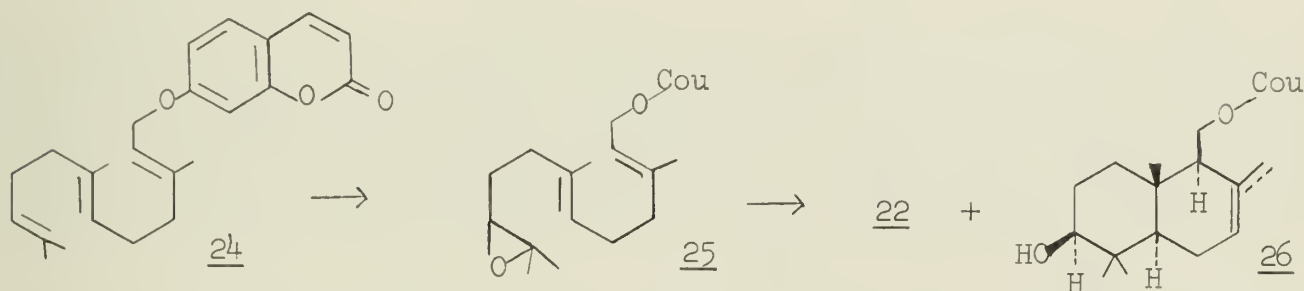
On treatment with boron trifluoride etherate in benzene, the epoxide was transformed into a variety of products. Column chromatographic purification of the products showed a modest yield of bicyclic diol monoacetate, and glpc indicated the presence of 85% stereoisomer 20a and 15% of the epimer 21a.¹³ However, if the cyclization was conducted in 85% phosphoric acid, the product consisted of 85% 21a and 15% 20a.

When cyclization of methyl farnesate epoxide (19b) was carried out¹¹ in boron trifluoride etherate-benzene solution and phosphoric acid, 20b and 21b were formed in modest yield (20-30%).

The first application of the cyclization reaction of the synthesis of natural products is found in the synthesis of sesquiterpene farnesiferols C (22) and A (23).¹⁴

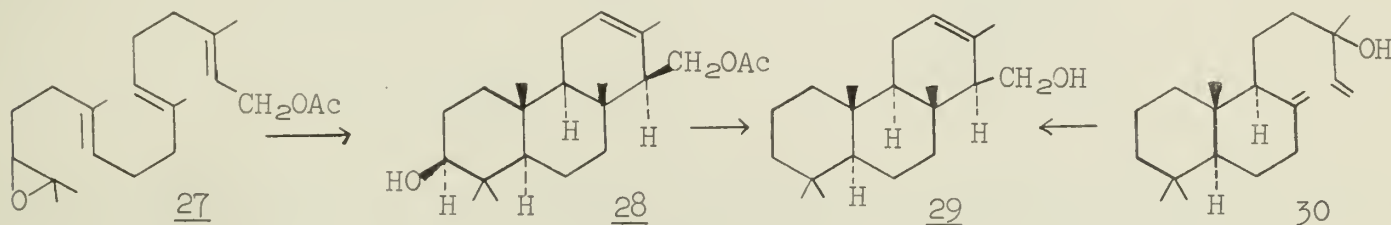


Terminal oxidation of umbelliprenin (trans,trans) (24) yielded epoxide 25 which was treated with boron trifluoride etherate in benzene. The cyclization reaction gave various products including bicyclic alcohols 26 (9%) and 22 (8%). Careful

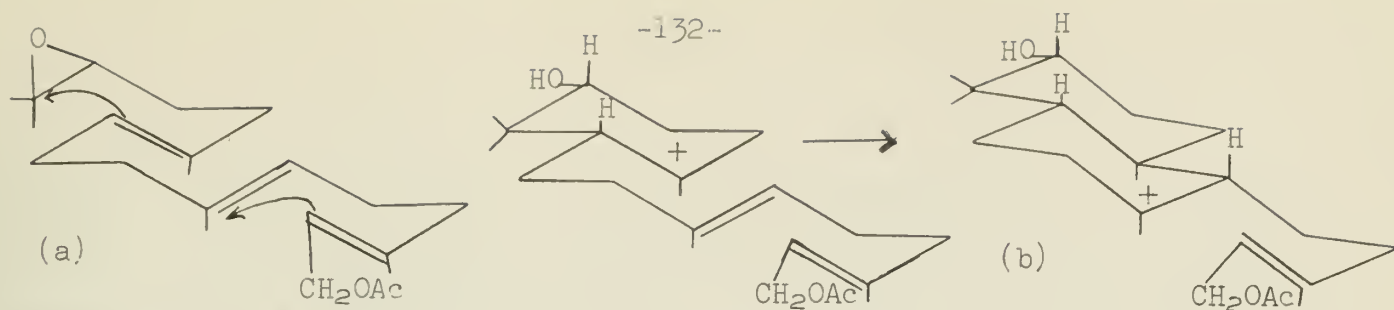


glpc inspection indicated that 23 is not the same as 26, and the assumption was made that farnesiferol A does not possess the normal trans-anti stereochemistry, but belongs, as tentatively suggested by Arigoni and Jeger,¹⁵ to the uncommon trans-syn class. Farnesiferol A (23) was synthesized from trans,cis-umbelliprenin in low yield.

Cyclization of trans,trans,trans-geranylgeranyl acetate epoxide (27) afforded the first example of a tricyclic cyclization.¹⁶ Trans,trans,trans-geranylgeraniol was prepared by homologation of trans,trans-farnesol. Oxidation of the diterpenoid acetate by NBS followed by treatment with base resulted in 27, which was cyclized by exposure to SnCl_4 in benzene to yield 28 (10% yield). The molecular structure and stereochemistry of 28 were established by conversion to 29 which was prepared independently from naturally occurring manool (30).

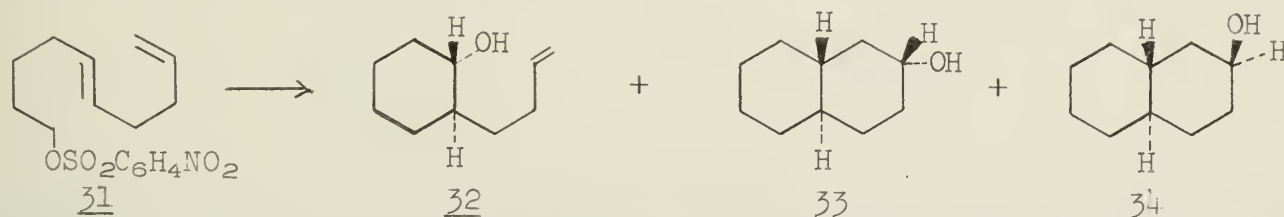


In the sesquiterpene series, it has been demonstrated¹⁷ that monocyclic products obtained by cyclization of terminal epoxides are not intermediate along the reaction pathway to the bicyclic products. This result was shown by the fact that the monocyclic products were not converted under original cyclization conditions to the bicyclic products formed concurrently from the epoxide. Consequently it is believed that 28 arises from epoxide 27 by (a) a synchronized cyclization, (b) a stepwise sequence involving mono or bicyclic carbonium ions or (c) a sequential combination of mechanisms (a) and (b). Cyclization of squalene 2,3-oxide was also carried out by treating the epoxide with 0.2 mole of stannic chloride in benzene at 10° for 5 minutes.¹⁸ The reaction yielded tricyclic alcohols as major products.

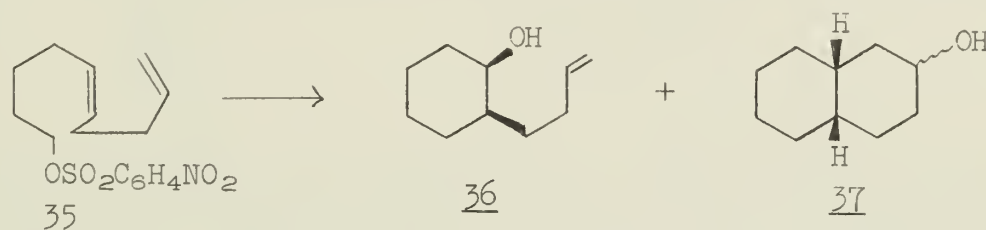


CYCLIZATION INVOLVING SOLVOLYSIS OF OLEFINIC SULFONATE ESTERS

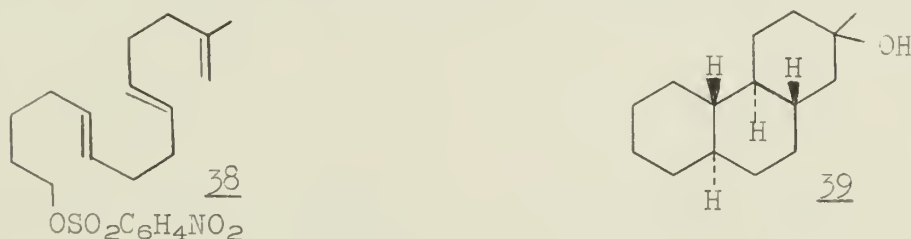
The acetolysis¹⁹ or formolysis²⁰ of 5-hexenyl *p*-nitrobenzenesulfonate proceeds with rate enhancement due to participation of the olefinic bond. Ring closure produces the corresponding ester of cyclohexanol in high yield. With this promising result, Johnson and coworkers examined the formolysis of *trans*-5,9-decadienyl *p*-nitrobenzenesulfonate (31).^{20,21} To facilitate analysis, the solvolysis products were treated with LiAlH₄ to cleave the formate ester. The total yield of alcohols



was 62% based on the starting sulfonate ester. The alcohol mixture was shown to contain 57% of 32, 14% of 33, 5% of 34 and some other alcohols, but no detectable amount of *cis* ring-fused alcohols was found. The solvolysis product of the *cis* sulfonate ester 35 afforded an alcohol fraction (68% yield) composed of 56% of 36, 13% of 37 and some other alcohols, none of which corresponded to *trans* ring-fused



product.²¹ Since the cyclization of the two isomeric sulfonate esters 31 and 35 proceeded in exactly the opposite stereochemical sense, the cyclization reaction must either be a concerted process or involve cationic intermediates which retain



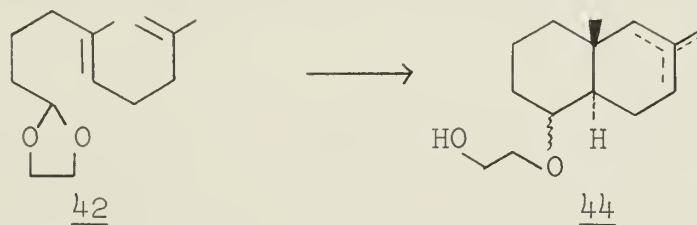
their stereochemistry. The acetolysis of the trienyl sulfonate ester 38^{22,23} was also examined by Johnson. The product consisted of ca 20% acyclic, 40% monocyclic, 8-12% bicyclic, and 2.8% tricyclic material. After treatment with LiAlH₄, the tricyclic product was shown to be exclusively the *trans,anti,trans* alcohol 39. Thus the formation of tricyclic material was highly stereoselective even though the yield was low.

CYCLIZATION OF OLEFINIC ACETALS

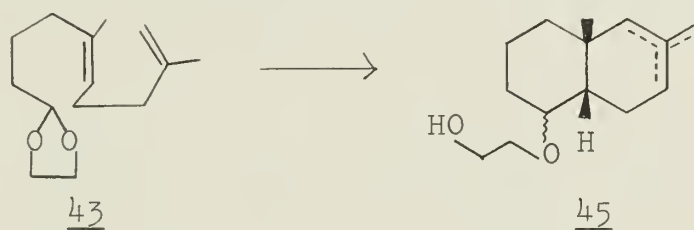
The tendency of certain unsaturated aldehydes to undergo acid-catalyzed cyclizations²⁴ led Johnson and coworkers to believe that the aldehyde group could be used to initiate polycyclization of polyolefinic systems. The acid-catalyzed cyclization of 5-methyl-5-hexenal (40) in methanol was shown to proceed through the acetal 41.²² This acetal yielded the cyclized products with longer reaction time.



In order to determine whether the stereochemical course of the reaction was dictated by the configuration of the olefinic bonds in the substrate, Johnson and coworkers studied the cyclization of trans and cis dienic acetals 42 and 43.²⁵ The trans dienic acetal 42, on treatment with stannic chloride in benzene, yielded trans-bicyclic

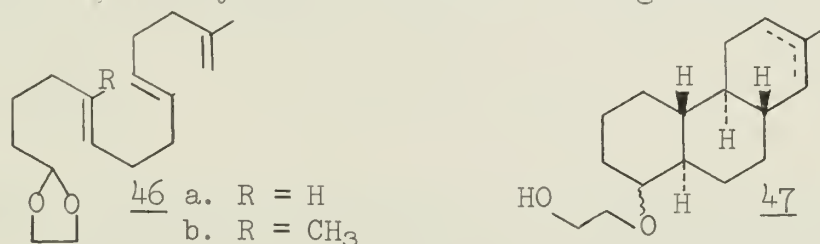


materials 44 in over 90% yield. The major component was $5\beta, \Delta^2$ -44. The products from cyclization of the cis acetal 43 were similarly composed mainly of bicyclic materials 45 in 88% yield. Identification of products was carried out by converting

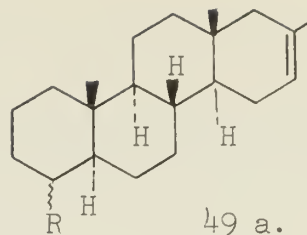
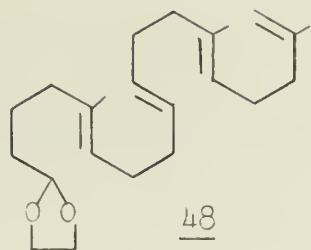


them to hydrocarbons which were then identified by comparison with authentic specimens prepared by independent synthesis. Since there is no stereochemical crossover in the cyclization of the two isomeric acetals, the process is stereospecific and must either be synchronous or involve cationic intermediates that maintain their stereochemical integrity.

Cyclization of acetal 46a appears to be the first example of the stereoselective synthesis of a tricyclic system of "natural" configuration as the major product.²³



When the cyclization reaction was carried out with stannic chloride in benzene, tricyclic alcohol 47 was produced in fair yield and with high stereoselectivity. Cyclization of the trienic acetal 46b was also examined.²² This reaction proceeds much more rapidly than the cyclization of 46a, and the yields of tricyclic material appear to be higher. Recently Johnson²⁶ reported that the tetraenic acetal 48 will undergo cyclization in stannic chloride pentane solution to afford tetracyclic materials 49a and 49b in about 30% yield. This, in turn, is the first reported case of nonenzymic stereoselective conversion of an acyclic molecule having no centers of symmetry into a product with four carbocyclic rings and a multiplicity of asymmetric centers.



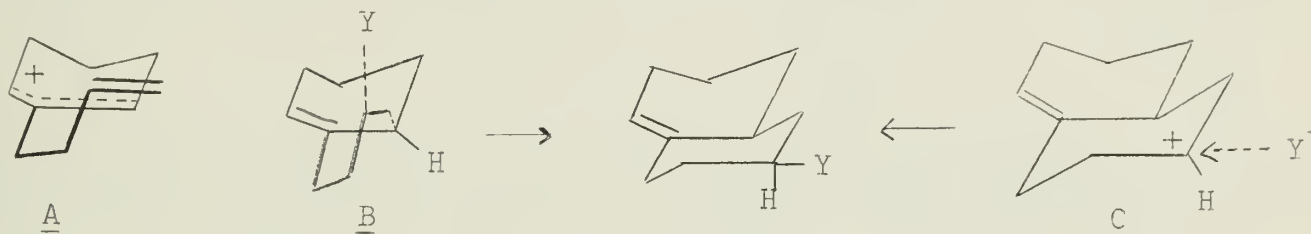
a. $R = \beta\text{-OCH}_2\text{CH}_2\text{OH}$
b. $R = \alpha\text{-CCH}_2\text{CH}_2\text{OH}$

ALLYLIC CATION PROMOTED CYCLIZATION

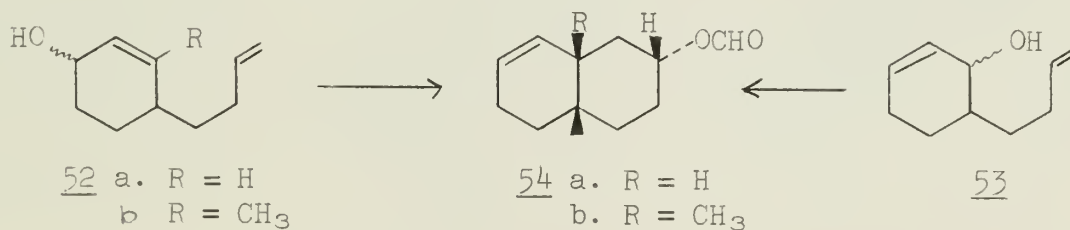
The first allylic cation system to be examined was the dienol 50, which on treatment with formic acid at room temperature underwent stereoselective cyclization. The reaction mixture was made alkaline and octanol 51 was found in about 85% yield.²⁷



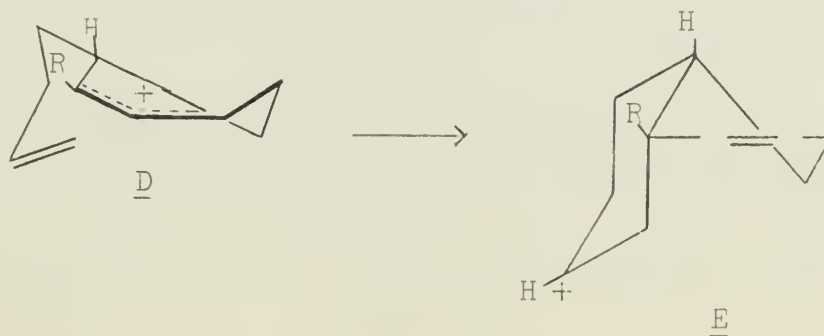
The stereoselective formation of 51 may be rationalized as a rapid ionization to the allylic cation A followed by a synchronous ring closure and attack by nucleophile as shown by formula B. Alternatively, the process could be stepwise, giving cation C which undergoes preferential equatorial attack by the nucleophile Y.



The cyclization of 52a and 53 were also studied, and it was found that these two isomers yield an identical major product 54a in ca. 50% yield.²⁸ It was shown that

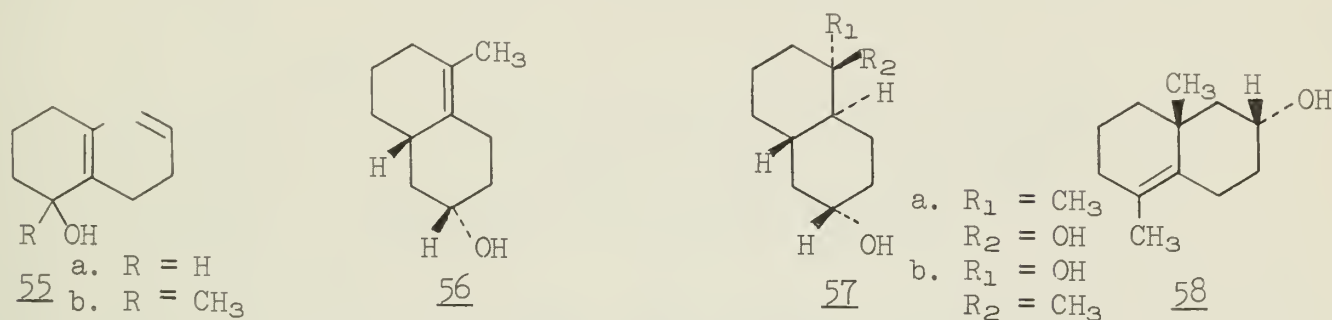


the epimer (cis-anti) of 54a was also formed in 10% yield. Cyclization of 52b²⁹ gave 54b in 90% yield. The stereoselective formation of 54 may be envisaged as proceeding via cations D→E, followed by nucleophilic attack at the equatorial position. The

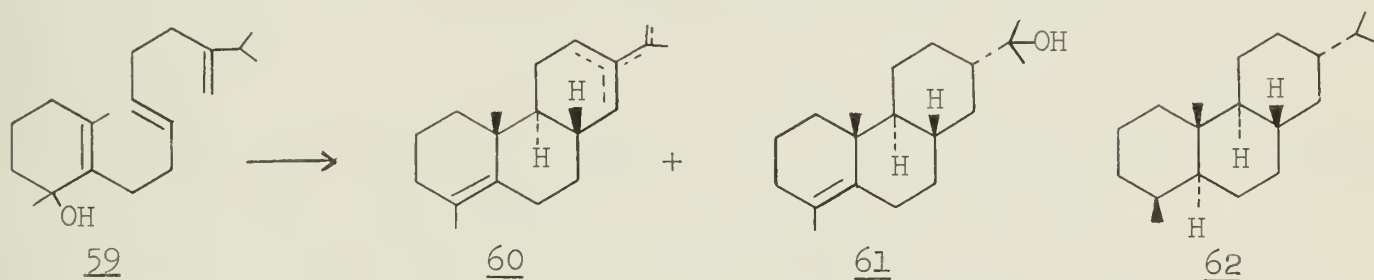


concerted mechanism of cation D does not play an important part, because the attack of solvent is not stereospecific.

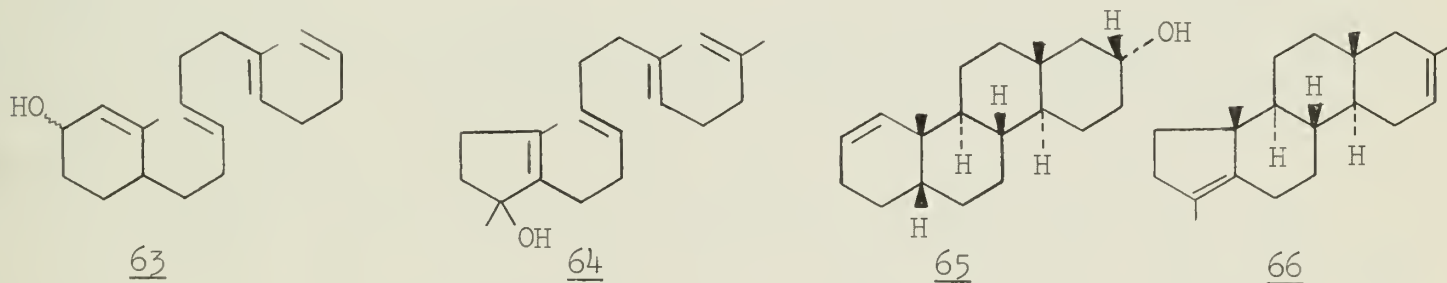
When the cyclization of dienol 55a²⁹ and 55b^{30,31} was carried out, it was found that the dienol 55a gave no product with an angular methyl group. Instead, 56, 57a and 57b were found as the major components in yields of 30, 35, and 22%, respectively.



Under the same conditions, 55b gave the cyclized product 58 in 79% yield. On shaking with formic acid, the trienol 59 was converted essentially into tricyclic materials 60 and 61 in 67% and 28% yield, respectively.³² These substances were all shown to



belong to the same stereochemical series by interconversion experiments and by their transformation into the naturally occurring fichtelite (62). Cyclization of tetraenol 63²² and 64³³ were recently studied and 65 and 66 were obtained in good yield.



SUMMARY

The stereochemical course of the cyclization involving polyolefinic epoxides, sulfonate esters, acetals, and allylic alcohols is dictated by the configuration of the substrates according to the Stork-Eschenmoser hypothesis. A concerted process and a stepwise mechanism involving cationic intermediates which retain stereochemistry have been suggested for the cyclization. Even tri- and tetracarbocyclic products with "natural" configuration have been obtained by the cyclization.

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6a-THIOTHIPHENE CHEMISTRY

Reported by Craig D. Tipton

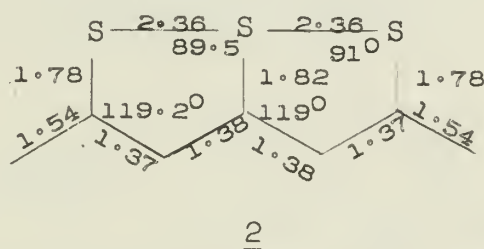
January 13, 1969

INTRODUCTION

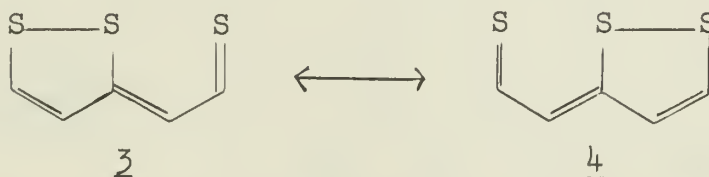
The first thiothiophthene was prepared by Arndt and his co-workers in 1925.¹ In their preparation they treated diacetylacetone with phosphorus pentasulfide in refluxing benzene, and structure 1 was assigned to the orange crystalline solid which they



obtained in 40% yield. In 1957 a 40 MHz nmr study of Arndt's product by Bothner-By and Traverso² showed that the vinylic protons and the methyl groups were equivalent on the nmr time scale. These workers concluded that the evidence supported the symmetrical structure 1. However, in 1958 Bezzi, Mammi, and Garbuglio³ published the X-ray structure 2 of Arndt's compound, which established a new and completely different structure for the molecule. In order to explain the equal sulfur-sulfur interatomic



distances and the nearly equal carbon-carbon bond lengths between the five nuclear carbon atoms these workers proposed that the molecule was aromatic. In their concept the structure of the nucleus was a resonance hybrid of the two limiting resonance structures 3 and 4. They adopted the term "no-bond resonance" to describe the



system. As an illustration of the aromaticity of the molecule they compared the bond lengths of 1.37 Å and 1.38 Å to the 1.39 Å bond lengths in benzene.

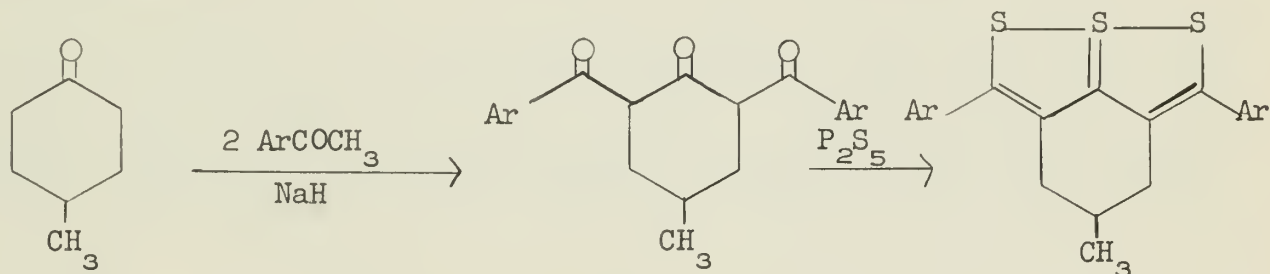
Recently, Maeda⁴ has introduced a different concept of the bonding. In his model the central sulfur atom is considered to be tetravalent. This model is superior in explaining certain aspects of the bonding and chemistry of the molecule; however, the bonding in the system cannot yet be regarded as fully settled. For the purpose of simplicity the structure 5 with the numbering system illustrated will be used in this seminar to represent the thiothiophthene system when bonding is not of prime interest.



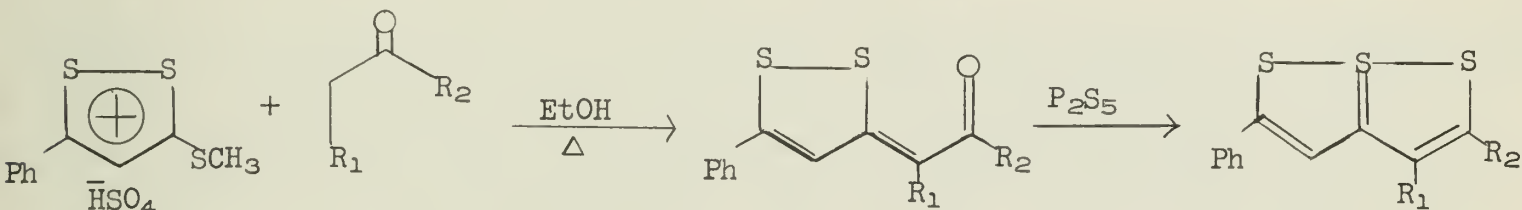
The name thiophiophthene is generic, but it is commonly used in the literature. However, Hertz, Traverso, and Walter⁵ have recommended the name meribicyclo-1,3-epidithiopentadien-5-thial based on structure 6. Stavaux and Lozac'h⁶ prefer the name trithia-1,6,6aS^{IV}-pentalene based on structure 5.

SYNTHETIC ROUTES TO THE THIOTHIOPHTHENES

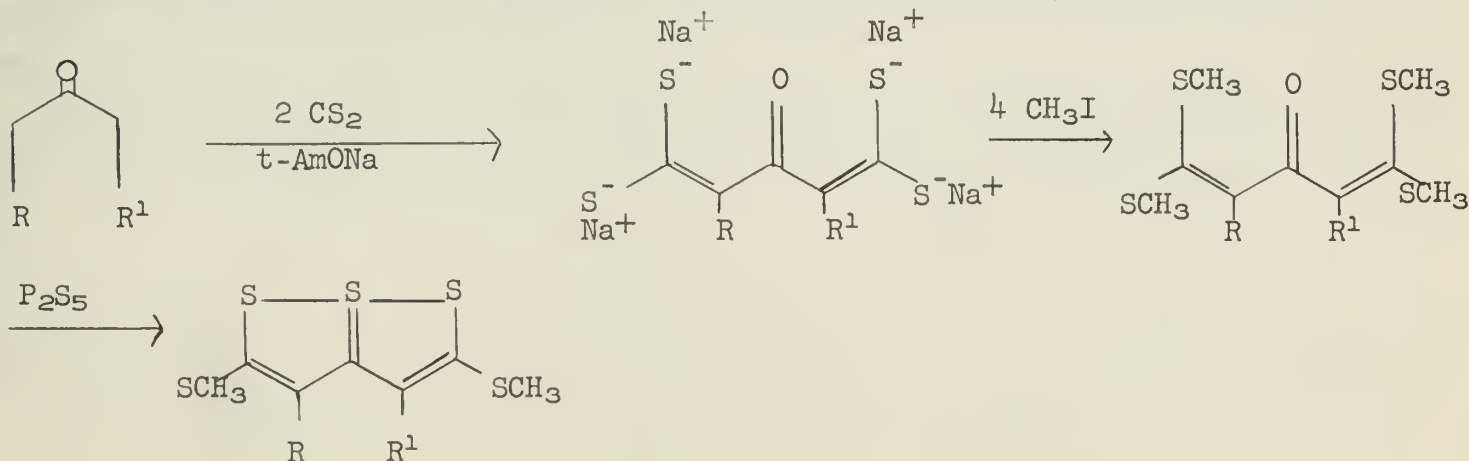
There are several general methods of preparation of the thiophiophthene system. The historical method of Arndt has been developed by Lozac'h and co-workers.⁶ They were able to prepare a variety of differently substituted triketones by condensing an alkyl or aryl ketone with an aromatic ester using sodium hydride in 1,2-dimethoxyethane. The triketones were then sulfurized with phosphorus pentasulfide to give the thiophiophthene. However, yields on the sulfurization reaction tended to be low (15-40%).



One of the most useful methods of preparation involves the condensation of a 3-methylthio-1,2-dithiolium salt⁷ with the activated methylene group of a ketone.^{8,9,10} This gives a dithiolyldene ketone which can be easily converted to the thiophiophthene by sulfurization with phosphorus pentasulfide. In the condensation the yields of the dithiolyldene ketone are generally around 40%.

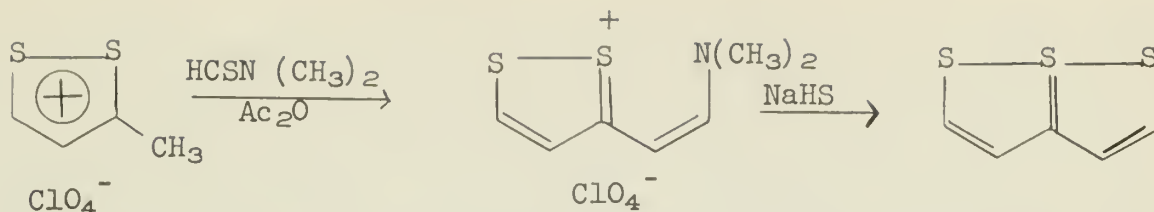


Another route to the thiophiophthene system has been described by Thullier and Vialle.¹¹ In their preparation two moles of carbon disulfide are condensed with a ketone. The condensation reaction with carbon disulfide can be carried out either simultaneously or in a stepwise manner. This synthesis, however, has the limitation



of leading only to 2,5-bisalkylthio derivatives.

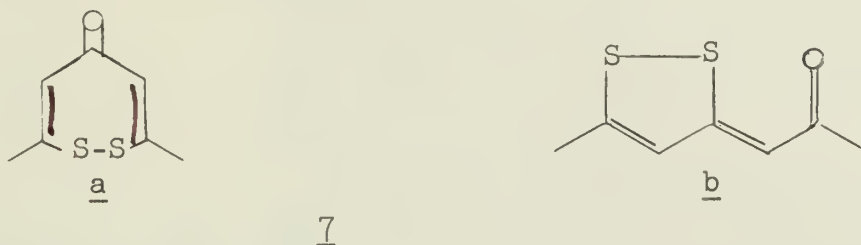
In a recent paper Reid and co-workers¹² have presented a synthetic route which starts with a 3-methyl-1,2-dithiolium salt. The methyl group in a salt of this type is reactive¹³ and may be condensed with dimethylthioformamide to give a Vilsmeier salt. This salt may then be caused to react with sodium hydrogen sulfide to give the thiophiophthene. Behringer and Grimm¹⁴ showed that β -diketones and α -acetylenic ketones give thiophiophthenes when treated with thioacetic acid and sodium acetate, and Lozac'h



and co-workers^{8,15,16} discovered that treatment of $\alpha,\beta,\gamma,\delta$ -unsaturated malonic esters or ketones with sulfur give the dithiolylidene ester or ketone. These can be converted to the thiothiophene by sulfurization with phosphorus pentasulfide. Other methods of synthesis have also appeared in the literature.^{17,18,19}

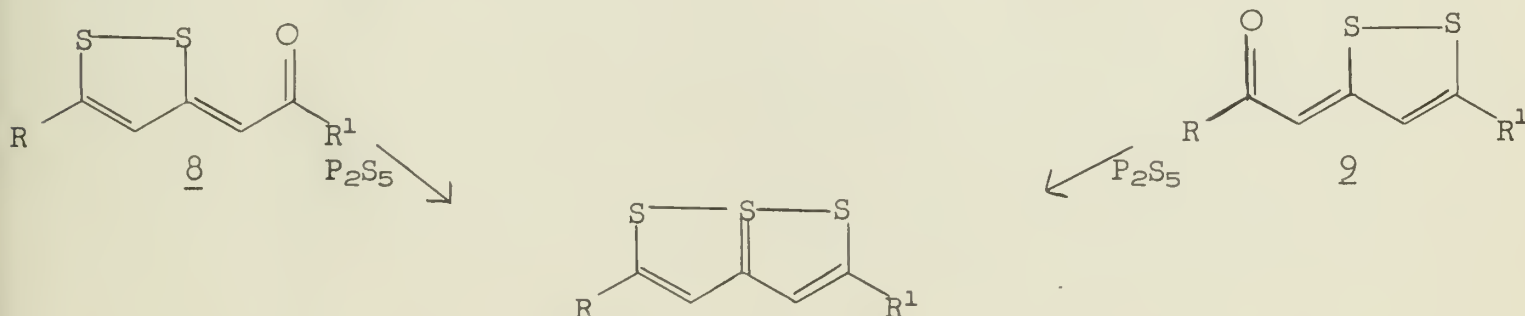
STRUCTURE AND BONDING

Arndt's original structure 1 for his reaction product stood until 1958 when Mammi published the X-ray structure of 2,5-dimethylthiothiophene which showed the linear arrangement of the sulfur atoms in the system. At about the same time several other workers presented chemical evidence that the structure of Arndt's compound was incorrectly formulated. Guillouzo²⁰ studied the infrared spectrum of the related oxygen compound 7. The carbonyl frequency came in the region $1550\text{-}1600\text{ cm}^{-1}$ which is the



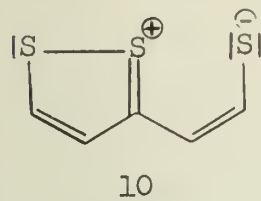
region for a chelated ketone or a β -diketone. This band disappeared on treatment with phosphorus pentasulfide. Guillouzo suggested that these data could be better explained by a dithiolylidene-ketone type structure 7b than the thiopin structure 7a. Hertz, Traverso, and Walter²¹ proposed that the chemical unreactivity of the thio-carbonyl group to 2,4-dinitrophenylhydrazine in Arndt's structure was further evidence that the structure was incorrect. These workers also did a nmr study of the dithiolylidene ketone 7b and 2,5-dimethylthiothiophene. They found the methyl groups and the vinyl protons to be equivalent on the nmr time scale in the thiothiophene, but not in the dithiolylidene-ketone as would be expected from the structure 7a. Finally, Behringer and co-workers²² found that desulfurization of the oxo-compound 7 with Raney nickel resulted only in heptan-2-one, thus eliminating any possibility of the thiopin structure 7a.

Pfister-Guillouzo and Lozac'h⁶ in an interesting experiment demonstrated the overall symmetrical nature of the thiothiophene ring system. They showed that sulfurization of the two isomeric ketones, 8 and 9, led to the same thiothiophene in each case.



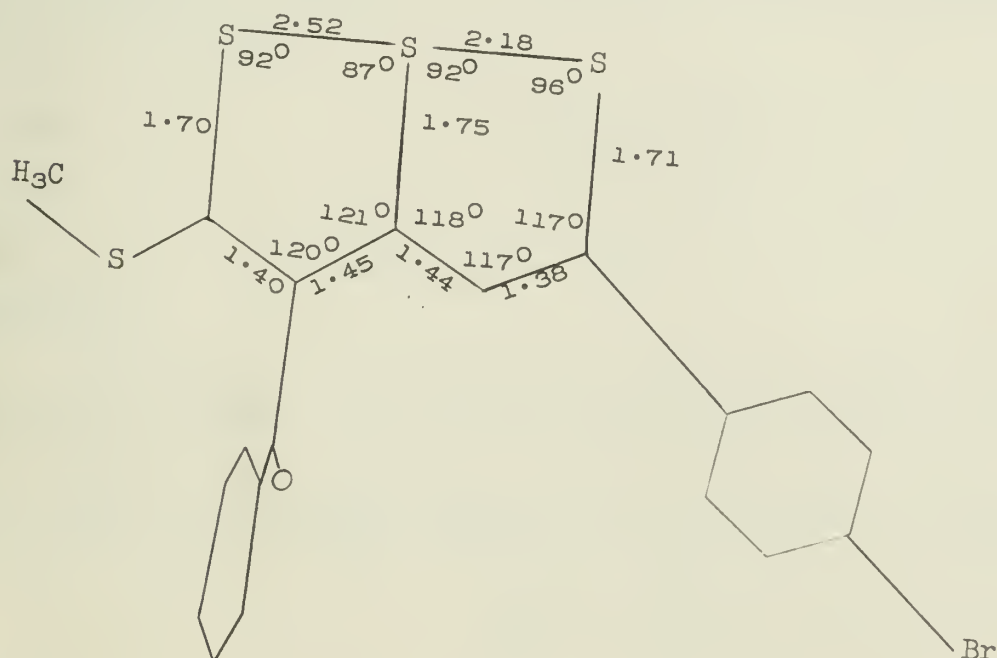
The X-ray structure 2 of Mammi and co-workers indicated from an analysis of bond lengths that the 5 nuclear carbon atoms were involved in an aromatic system. This contention has been supported by the value of 7.53 ppm for the chemical shifts of the protons at the 3 and 4 positions of 2,5-dimethyl-6a-thiothiophene.²³ The

sulfur-sulfur bond lengths are equal in length (2.36 Å), and the sulfur-sulfur bond order is less than unity since the value for normal disulfide bonds is 2.00-2.10 Å. The carbon-sulfur bond length is 1.71 Å compared with 1.81 Å for a carbon-sulfur single bond and 1.55 for a carbon-sulfur double bond. As a result of their observations Mammi and co-workers proposed the "no-bond resonance" scheme 3,4 to represent the bonding in 2,5-dimethyl-6a-thiothiophthene. The "no-bond resonance" structure accounts for the bond lengths of the five nuclear carbon atoms and the less than unity sulfur-sulfur bond lengths. From this model one would also predict that any symmetrically substituted 6a-thiothiophthene should have equal sulfur-sulfur bond lengths, which is a conclusion that is still in doubt.²⁴ The model also accounts for the unreactivity of the thiocarbonyl group. Instead of a resonance hybrid of the two structures 3 and 4, the unusual features of the 6a-thiothiophthene was suggested by Leaver and McKinnon²⁵ as possibly due to a rapid tautomerism between the two structures. However, this is unlikely when the lack of thiocarbonyl reactivity and the X-ray structure are considered.²⁴ Giacometti and Rigatti²⁶ have discussed the electronic structure of the molecule based on the "no-bond resonance" structure. In their calculations they assume that the sulfur atoms use only p-type orbitals for bonding. They arrived at the polar structure 10 as the simplest possible classical formula with

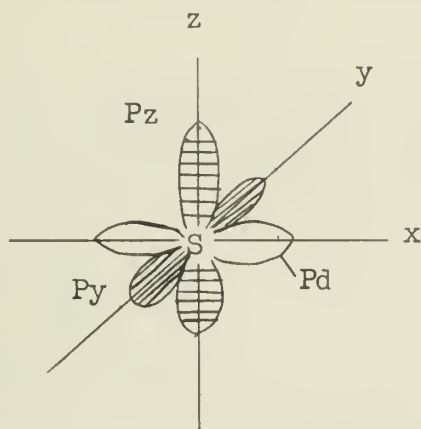


bivalent sulfur atoms. Their calculations suggested that the central sulfur atom is highly electron deficient and that the central carbon-sulfur bond should be slightly longer than the two outer carbon-sulfur bonds. It was claimed that these conclusions were all in accord with the X-ray structure of Mammi.

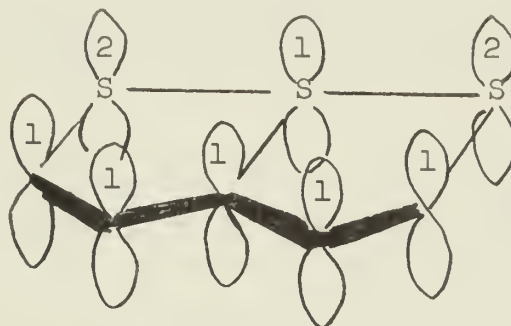
Recently, the X-ray structure of the unsymmetrical 3-benzoyl-5-p-bromophenyl-2-methylthio-6a-thiothiophthene (11) has been published by Beer, Paul, and co-workers.²⁷ In this example the sulfur-sulfur bond lengths are unequal but still much less than the sum of the van der Waals radii of sulfur (3.70 Å). In the crystal, neither the p-bromophenyl group nor the carbonyl group is conjugated with the 6a-thiothiophthene system, as the twist angles are 32° and 79°, respectively. Another important feature of this structure is the nearly equal outer carbon-sulfur bond lengths. If "no-bond resonance" is a major contributor to the structure of this molecule, then the unequal sulfur-sulfur bond lengths should also be reflected in the outer carbon-sulfur bonds, but this is not the case.²⁴



An alternative picture of the bonding has been proposed by Maeda²⁸ whose treatment of the bonding is more rigorous than "no-bond resonance". In Maeda's model one of the p-electrons in the central sulfur atom is promoted to a d-orbital forming a pd hybrid orbital at the central sulfur atom (12). The central sulfur atom now tetravalent can then form a σ bond to each end sulfur atom by means of the two pd hybrid orbitals. The P_y orbital is used to form a σ bond to the central carbon atom, and the P_z orbital

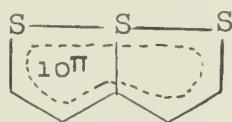


12



13

can be used to form a π bond with each end sulfur atom. The π system that is formed is completely delocalized and extends around the perimeter of the molecule. The above diagram 13 illustrates the system and the number of electrons donated by each atom to it. The delocalized system contains 10 electrons and assuming Hückel's rule the system may be assumed to be aromatic. In another paper²⁹ Maeda sought to explain why the central sulfur atom is able to hybridize a p-orbital with a d-orbital, because normally the energy difference between these two orbitals is too great to allow hybridization. His explanation was that when the effect of the neighboring atoms is taken into account a contraction of the d-orbital results. This contraction allows the d-orbital to take part in the bonding. As a result of Maeda's model the structure 14 probably best represents the bonding in the molecule. An electronic structure such as this allows for a symmetric structure or an unsymmetric structure depending on other factors such as substitution.

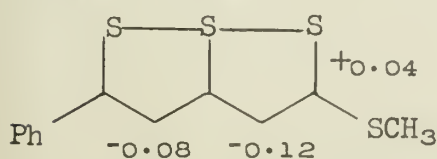


14

CHEMISTRY

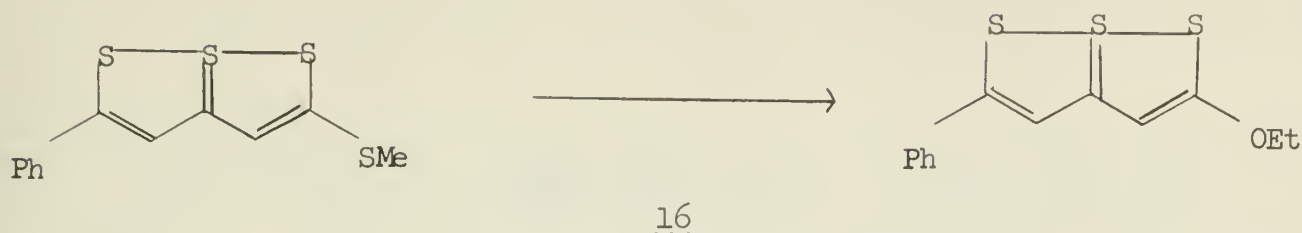
Little work has been done on the chemistry of the thiothiophene system until recently, as most of the earlier work has been directed towards synthesis of the ring system.

Johnstone and Ward³⁰ have calculated the charge densities for the 2,3, and 4 positions of 2-methylthio-5-phenyl-6a-thiothiophene using the Wheland-Mann ω -technique³¹ on Maeda's model. The results (15) suggested to them that the 2-position should be subject to nucleophilic attack and the 3-position should be subject to electrophilic attack. Beer and co-workers³⁰ have reported that the 2-methylthio group in 2-methylthio-5-phenyl-6a-thiothiophene is slowly replaceable by ethoxide (16), when the compound is refluxed in a solution of sodium ethoxide in ethanol.

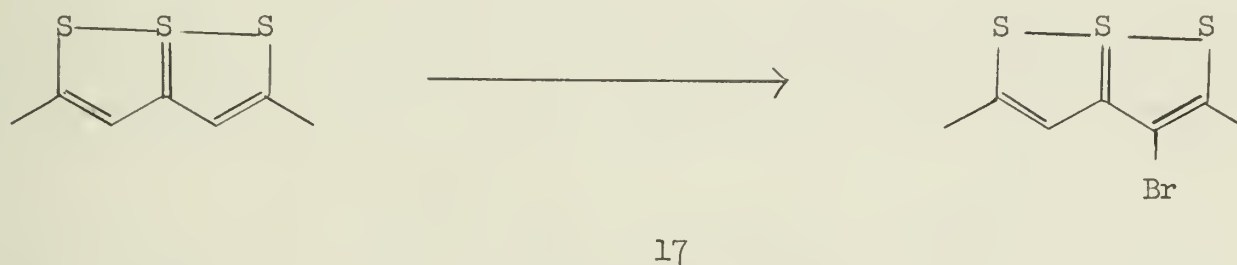


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This reaction also demonstrates the marked stability of the 6a-thiothiophthene system

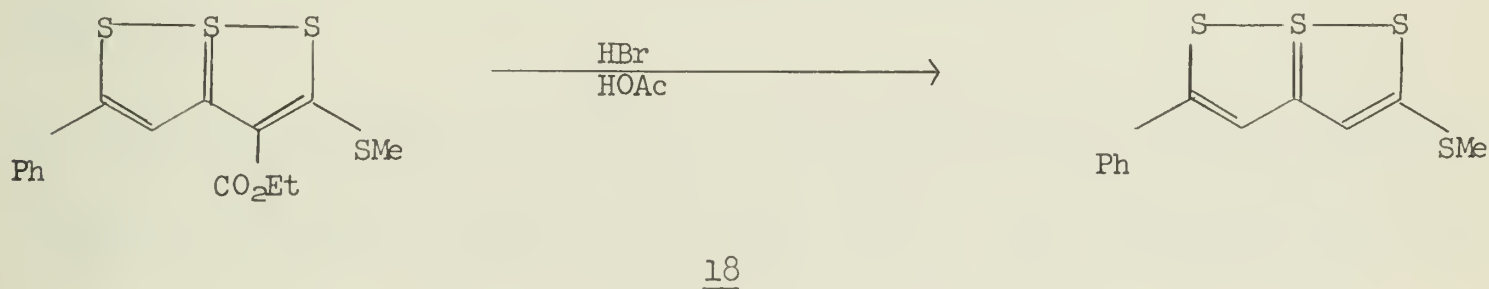


towards basic reagents. These workers have also brominated 2,5-dimethyl-6a-thiothiophthene with molecular bromine under normal conditions to give a mono-bromo derivative 17. Nitration of a 6a-thiothiophthene at the 3-position has also been reported, but

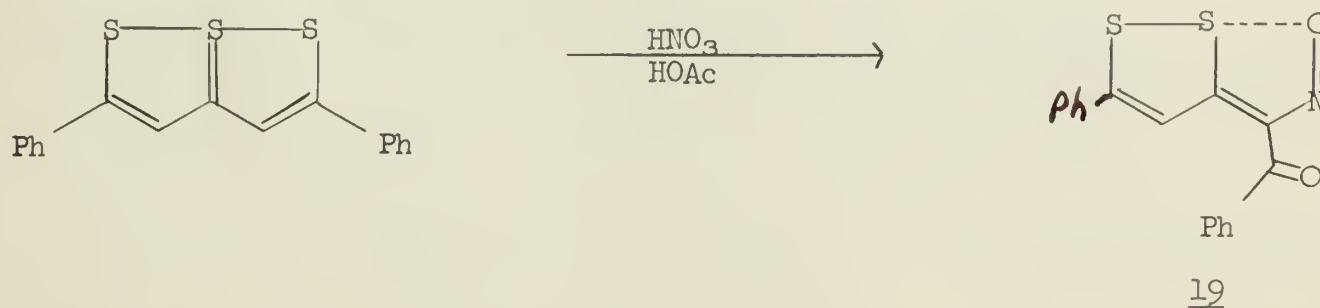


attempted acylations under Friedel-Crafts conditions have failed.²⁴ If one accepts the charge density argument of Johnstone and Ward, the example of nucleophilic displacement at position 2 and electrophilic substitution at position 3 have lent further support to Maeda's model of the molecule.

The 6a-thiothiophthene system also shows a marked stability toward acidic reagents. Beer and co-workers³² have reported the interesting simultaneous hydrolysis and decarboxylation of 3-ethoxycarbonyl-2-methylthio-5-phenyl-6a-thiothiophthene with HBr in refluxing acetic acid (18). The same group³⁰ has also reported that attempted

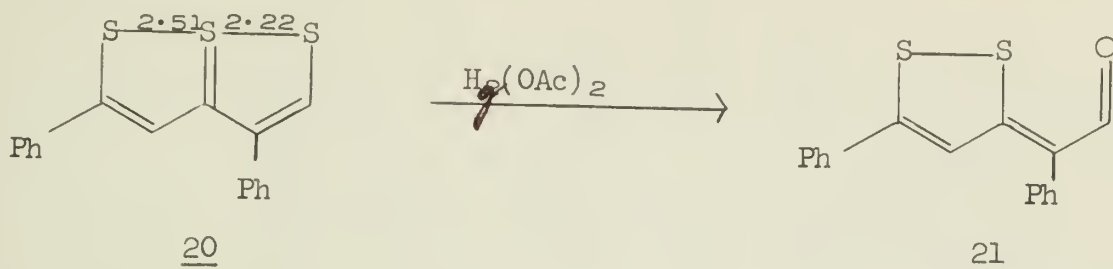


nitration with concentrated nitric acid in hot acetic acid gave a nitroso compound to which they assigned the structure 19 on the basis of the carbonyl absorption in the infrared. This compound may also be characterized by some bonding between the oxygen atom and the sulfur atom.



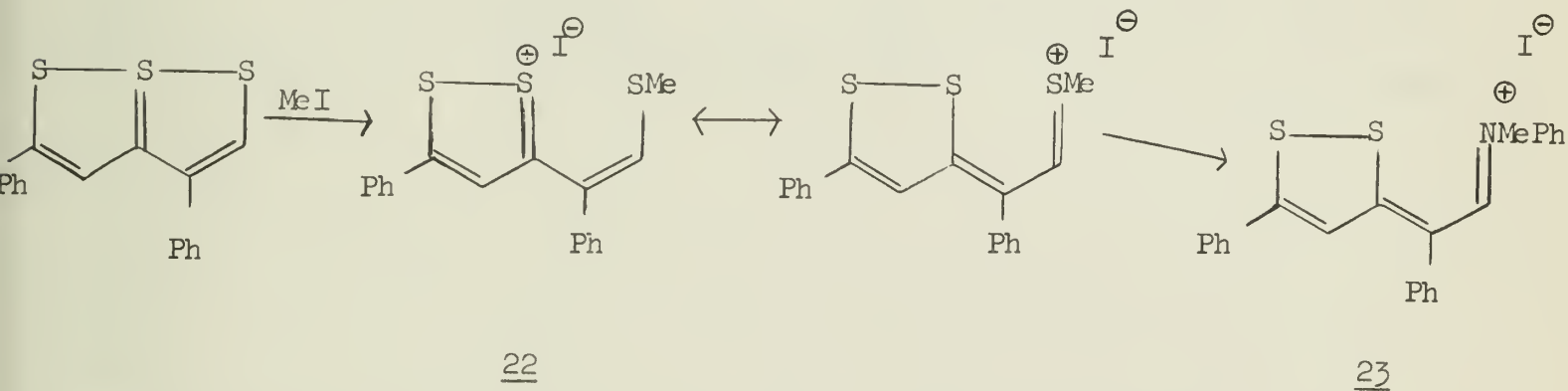
Many thiothiophthenes readily undergo oxidation with mercuric acetate to give the corresponding dithiolylidene ketone.^{8,24,25} Klingsberg³³ has oxidized the unsymmetrical

3,5-diphenyl-6a-thiothiophthene 20, whose sulfur-sulfur bond lengths have been determined by X-ray,³⁴ with mercuric acetate to give only one dithiolylidene ketone 21. The product results from the attack at the least hindered sulfur atom, and not the one



with the most thiocarbonyl character.

Cartwright²⁴ has reported that the sulfur atoms of 3-benzoyl 2-methylthio-5-phenyl-6a-thiothiophthene cannot be methylated by methyl iodide in nitromethane. However, Klingsberg³³ has reported that 3,5-diphenyl-6a-thiothiophthene reacts smoothly with methyl iodide to give a salt 22. This salt will react with a primary aromatic



amine to give an anil 23 with the elimination of methanethiol.

CONCLUSION

While the structure of a number of 6a-thiothiophthenes has been determined by X-ray analysis, the theoretical interpretation of the bonding is still in dispute. Recently a number of workers have begun to investigate the chemistry of the 6a-thiothiophthene ring system. They have discovered that the system has the unusual stability and typical reactions of an aromatic system. More investigation into this system is merited as it may shed light on the unusual bonding in the molecule.

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ORGANIC SEMINAR ABSTRACTS

1968-69

Semester II

Department of Chemistry and Chemical Engineering

University of Illinois

SEMINAR TOPICS

II Semester 1968-69

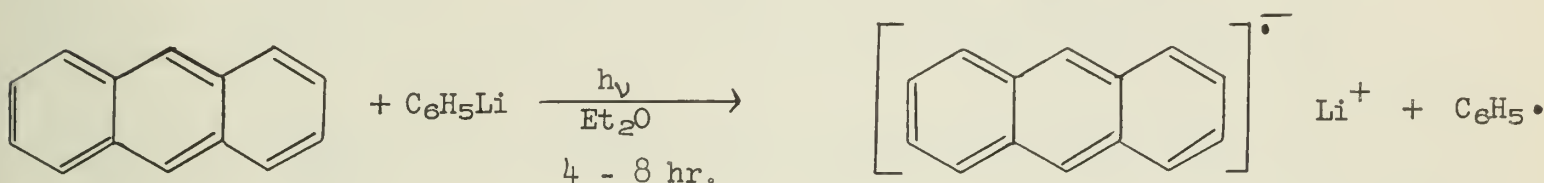
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PHOTOLYTIC REDUCTION AND ALKYLATION OF ANTHRACENE WITH ORGANOLITHIUM

Reported by William H. Harned

March 10, 1969

A book by Kaiser and Kevan reviews anion radicals very thoroughly.¹ There are a variety of methods in the literature for their preparation.²⁻⁴ Recently Winkler and Winkler prepared anion radicals by photolysis of polycyclic aromatic hydrocarbons and organolithium compounds in ether with a medium or high-pressure mercury lamp.⁵ The aromatic anion radical was identified by its esr spectrum. In a typical experiment on a preparative scale, from anthracene and phenyllithium there are obtained

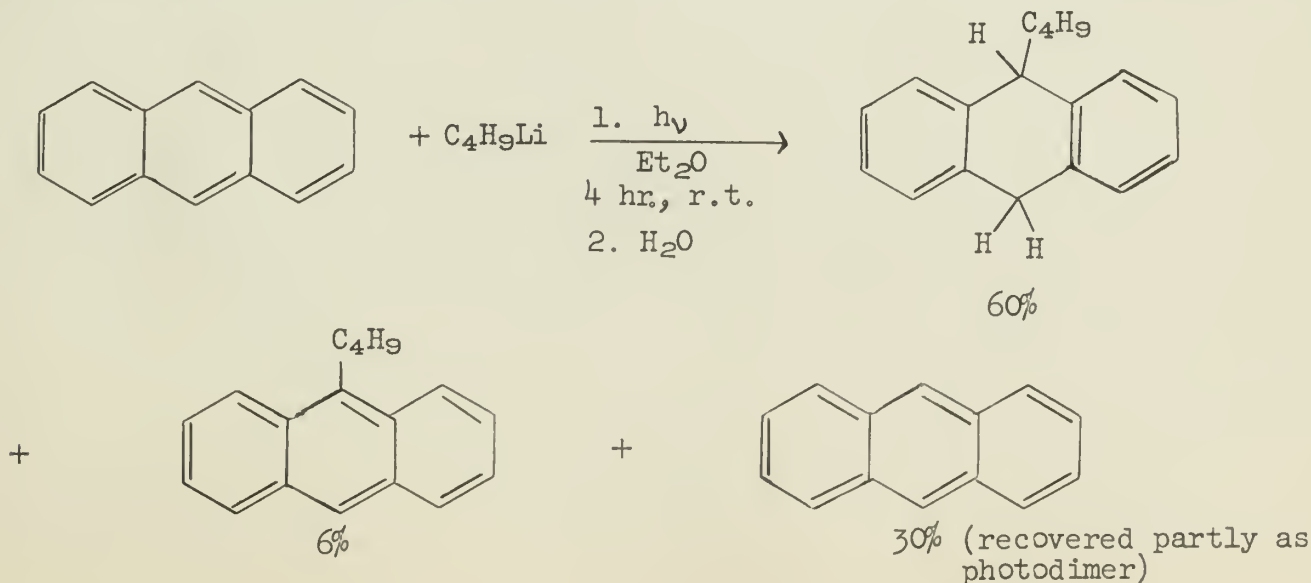


upon hydrolysis of the reaction mixture, anthracene (recovered), 80%; 9,10-dihydroanthracene, 17%; and biphenyl 27%, based on phenyl groups present initially as phenyllithium. This method has several advantages over many of the methods previously used. The organolithium scavenges water which destroys radical anions and oxygen which broadens esr lines. There is no induction period. The concentration of radical anions can be controlled by the time of exposure to irradiation. Also there is relative freedom in the choice of solvent.

Two possible schemes have been postulated for the reaction of anthracene and phenyllithium upon irradiation. The light could promote a pi electron of anthracene to an antibonding orbital ($\pi \rightarrow \pi^*$) leaving a low energy bonding orbital vacant. This vacant orbital could accept an electron from the anion of phenyllithium to form an anthracene anion radical and a phenyl radical. An alternative pathway is a light-induced homolytic dissociation of phenyllithium to produce a phenyl radical and a lithium atom. This reaction has been observed to occur in ether.⁶ The lithium could then transfer an electron to an excited or unexcited anthracene molecule to form the radical anion.

The reaction to form the anion radical is believed to depend on both the oxidation potential of the anion of the organolithium and the electron affinity of the aromatic substrate. Photoexcitation of poor electron acceptors such as aromatic hydrocarbons increases their electron affinity.⁵

In the course of generating anion radicals via irradiation of anthracene in the presence of certain alkylolithium compounds, it was observed that upon hydrolysis of the reaction mixture, 9-alkyl-9,10-dihydroanthracene could be isolated.⁷ The extent



of alkylation is dependent on the nature of the alkyl group, solvent, and wavelength of irradiation. A variety of pathways for the reaction are possible.^{7,8}

The reaction of aromatic hydrocarbons with the isomeric butyllithiums in paraffin solvents at elevated temperature (65°-160°) has been reported.⁹ Alkylated products were obtained in yields of 15-50%.

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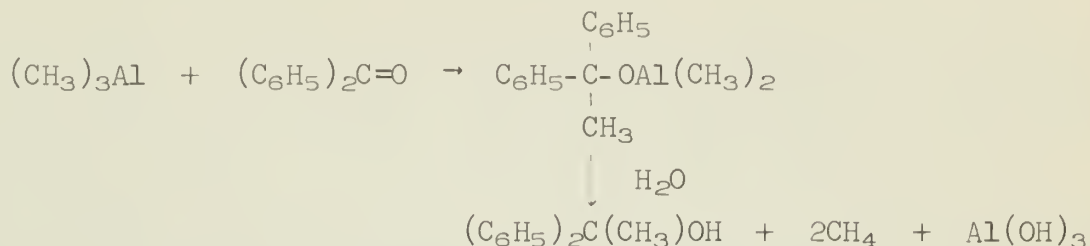
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Kinetics of the Addition of Trimethylaluminum to Benzophenone

Reported by Stephen E. Rudolph

March 20, 1969

The reaction between trimethylaluminum and benzophenone in benzene provides an ideal system for the study of organoaluminum alkylation reactions.^{1,2} In this



system no reduction or enolization products are possible and only one methyl group on trimethylaluminum is available for reaction. Trimethylaluminum exists in benzene as a bridged dimer^{3,4} but at normal temperatures the terminal and bridging methyl groups undergo rapid exchange, probably through dissociation to the monomer and recombination to the dimer.⁵

Upon mixing the benzophenone and trimethylaluminum a complex immediately forms which has a broad new absorption band between 270-500 mμ. The rate of reaction can be followed by the disappearance of this absorption due to complex or by quenching the reaction and observing the disappearance of ketone absorbance. The reaction is observed to be appreciably faster when the ratio $[(\text{CH}_3)_3\text{Al}]/[(\text{C}_6\text{H}_5)_2\text{C}=\text{O}]$ is 2:1 than when it is 1:1. In addition, when only a fractional excess of trimethylaluminum is present the reaction is fast until the excess is consumed and then becomes very slow. This suggests that the initially formed complex gives product faster by reaction with an additional mole of trimethylaluminum than by internal rearrangement. Thus two mechanisms are required for this reaction; one mechanism is operative when excess trimethylaluminum is present and the other when organoaluminum reagent and ketone are present in equal amounts.

When trimethylaluminum is in excess the reaction goes rapidly to completion and the kinetic data are best explained in terms of a scheme in which the rate-determining step involves reaction of complex with monomeric trimethylaluminum. When trimethylaluminum and benzophenone are present in equal amounts the complex decays by a first-order rearrangement but at the same time free ketone is regenerated from complex at about half the rate of complex decay. It is thought that this is due to the removal of trimethylaluminum from unreacted complex by product, $(\text{C}_6\text{H}_5)_2\text{C}(\text{CH}_3)\text{OAl}(\text{CH}_3)_2$, to form a product-trimethylaluminum complex and releasing free benzophenone in the process. At 50% reaction, then, there exists in solution a nearly equimolar mixture of free benzophenone and a complex of addition product with trimethylaluminum. The alkylation of the second half of the benzophenone then proceeds at a much slower rate.

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THE PHOTOCHEMISTRY OF AMIDES

Reported by Thomas S. Woods

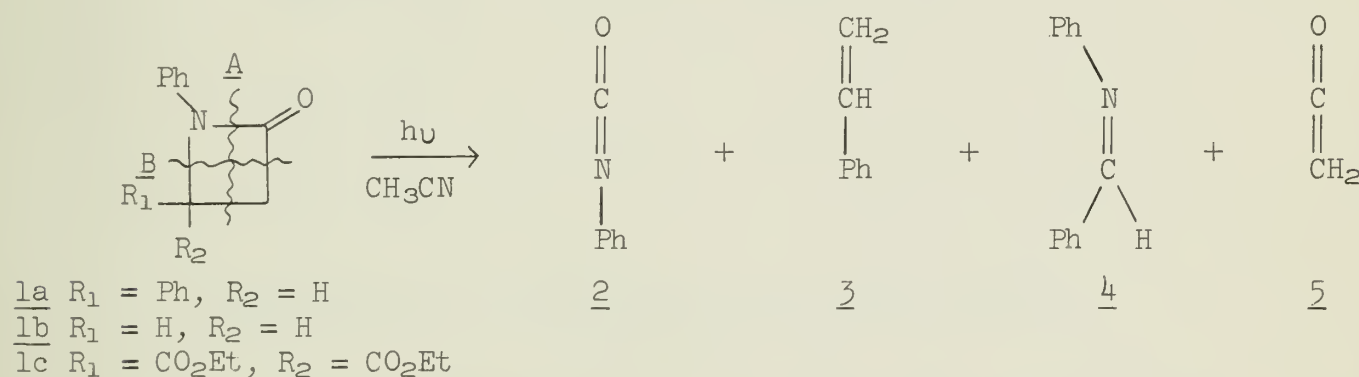
March 27, 1969

In spite of the importance of the amide functional group in ground state chemistry, its photochemistry has not been extensively studied.¹ Very little is known about the excited states of amides; consequently, little mechanistic work has been done in amide photochemistry.

The electronic absorption spectra of amides generally consist of two broad bands with vibrational fine structure in the regions of 130-160 m μ and 170-200 m μ .² These bands have been assigned to $\pi \rightarrow \pi^*$ transitions with a separate $n \rightarrow \pi^*$ transition buried under the longer wavelength band.²⁻⁴ The energy levels should be similar to those of esters, and the same types of transitions are noted in the electronic absorption spectra of both.^{3,5}

The photolysis of amides has been shown to promote homolytic cleavage of carbon-carbon and carbon-nitrogen bonds. For example, irradiation of gaseous acetamide has been shown to yield methane, ethane, carbon monoxide, ammonia, water, and acetonitrile.⁶ In aqueous solution, photolysis of acetamide yields acetic acid, ammonia, carbon dioxide, carbon monoxide, methane, and nitrogen.⁷ In the higher amides, 1-alkenes are prominent photoproducts, probably resulting from a Norrish Type II photoelimination.⁸

Martin Fischer has reported observing cleavages of both carbon-carbon and carbon-nitrogen bonds in the photolysis of β -lactams.⁹ He found that on pyrolysis 1a gave exclusively fragmentation pattern B to produce phenyl isocyanate (2) and styrene (3), whereas on photolysis 1a underwent fragmentation primarily by pathway A to give benzaldehyde anil (4) and ketene (5) in addition to a small amount of 2 (3 polymerized under the reaction conditions). Fischer found that the amounts of products produced from the two pathways could be varied by the presence of substituents on the molecule;



thus, 1b underwent photofragmentation to give products derived exclusively from pathway A, while 1c gave products only from fragmentation pattern B. Other substituents gave products which indicated that both pathways were proceeding.

Sensitization experiments led to the conclusion that both fragmentation pathways probably proceeded from the first electronically excited singlet state, although it is conceivable that pathway B could have arisen from a vibrationally excited ground state.

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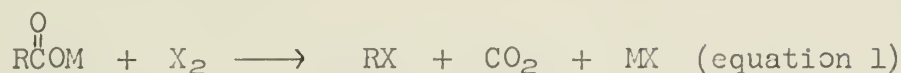
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THE HÜNSDIECKER REACTION

Reported by Lydia E. Moissides

April 10, 1969

The halogenative decarboxylation of metal salts of carboxylic acids (equation 1) is commonly known as the Hünsdiecker reaction.



M = Ag⁺, Hg²⁺, Na⁺ (Ag⁺ preferable); X₂ = Br₂, Cl₂, I₂ (Br₂ preferable)

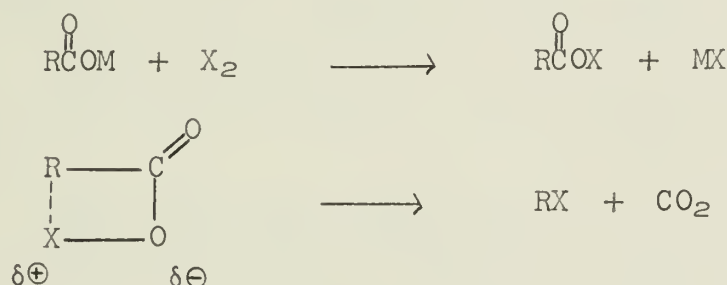
R = alkyl, aryl, etc.; Solvent = CCl₄, CS₂, C₆H₅NO₂, C₆H₆, n-C₅H₁₂

It has been used to prepare aliphatic, aromatic, alicyclic, and halosubstituted aliphatic halides, etc.¹⁻⁴ The practical disadvantage of the reaction is that the reagents used must be scrupulously dry in order to obtain satisfactory yields of alkyl halides.^{1,5}

The mechanism of the reaction has been subject to much study, and the mechanistic pathways (a)-(d) have been proposed--the intermediacy of an acyl hypohalite

(R $\overset{\text{O}}{\parallel}$ COX)⁶ has been assumed in all the work on the Hünsdiecker reaction:

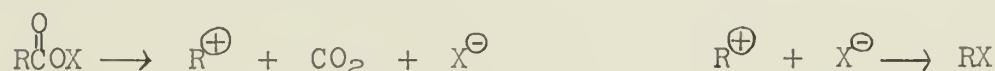
(a) Cyclic intramolecular rearrangement--S_Ei^{1,7}



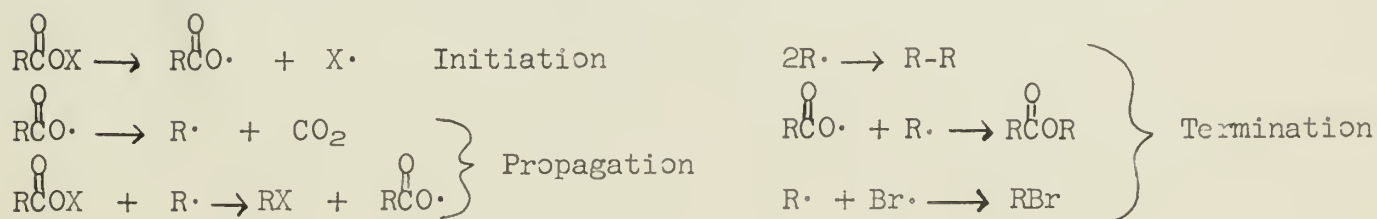
(b) Bimolecular electrophilic substitution--S_E2^{1,8}



(c) Carbonium ion mechanism^{9,10}



(d) Free radical chain reaction^{1,10,11}



Pathway (d) has received the most support experimentally.

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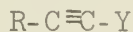
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YNAMINE CHEMISTRY

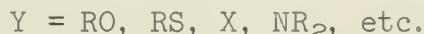
Reported by James E. Bittell

April 21, 1969

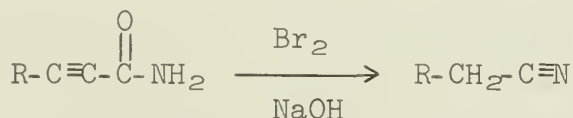
Ynamines are a new addition to a known class of derived acetylides in which the heteroatom (X, O, S, P, etc.) is directly attached to the triply-bonded carbon atom. Most ynamines are stable, clear liquids that can be routinely handled in



1



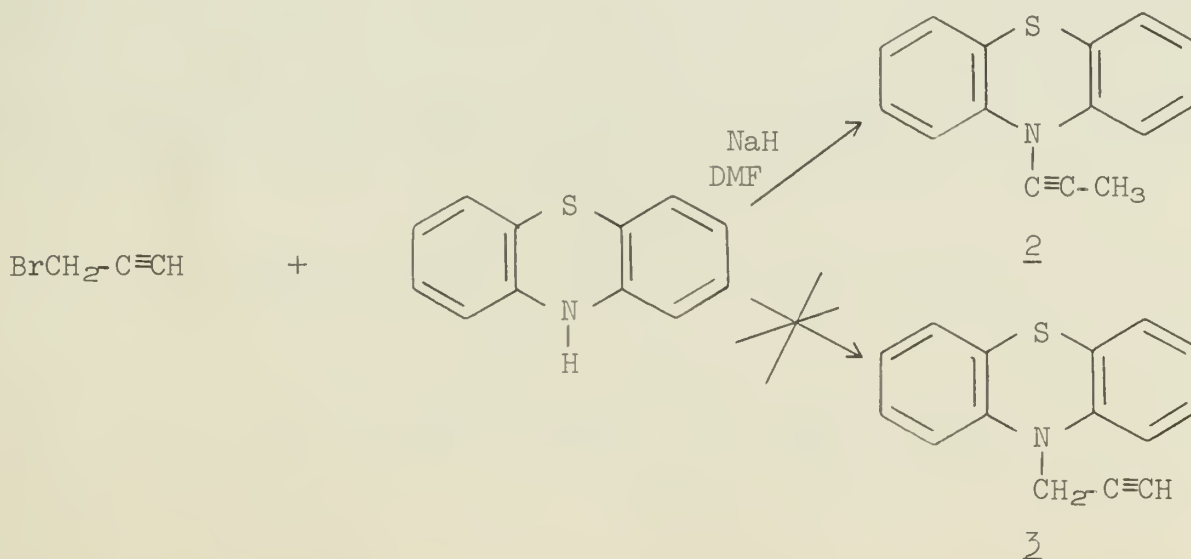
air and show no appreciable deterioration upon vacuum distillation. So far only ynamines with tertiary amino groups are known. All attempts at synthesis of ynamines with primary amino groups have led to the tautomeric nitriles.^{1,2} For example a Hoffmann degradation of an acetylene amide leads to a nitrile.



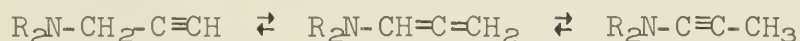
An interesting aspect of ynamine chemistry is that only in 1958 were these relatively stable compounds first synthesized. Several earlier reports of syntheses of ynamines have subsequently been shown in spectroscopic studies to be incorrect.³ J. Bode⁴ thought he obtained ethynyltrimethylammoniumhydroxide from $BrCH_2CH_2N(CH_3)_3^+Br^-$ by elimination of HBr, addition of Br_2 , and a second HBr elimination. It now appears more likely that he actually obtained $CH_2=C(OH)N(CH_3)_3^+Br^-$.³ F. Moulin⁵ reported the isolation of an ynamine from the reaction of a bromoacetylene with piperidine. He was apparently deceived by a small amount of piperidinium bromide dissolved in the organic phase which had the same nitrogen value as the sought-for product. Also, E. Ott and associates⁶ obtained from $ClC\equiv CCl$ and diethylamine not $ClC\equiv CN(C_2H_5)_2$ as reported, but $ClCH=C[N(C_2H_5)_2]_2$.

The useful preparative methods developed during the last five years fit into three general types: (1) the isomerization of propargyl derivatives; (2) the joining of the acetylene group to the substituent; and (3) the formation of the triple bond by elimination from a suitable amine.

The first ynamine, prepared accidentally by Zaugg, Swett, and Stone⁷ in 1958, was the result of the isomerization of a propargyl derivative. They obtained from propargyl bromide and phenothiazine the ynamine 2 instead of the expected N-propargylphenothiazine 3. This synthesis of an ynamine was considered doubtful until it



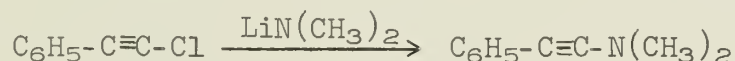
was substantiated by J. Dumont in 1965. Dumont⁸ found that under somewhat different conditions--methyl lithium in ether--the expected propargyl derivative is formed in good yield. It was then found that the propargyl derivative undergoes a facile prototropic isomerization to the ynamine with strong bases (KOH or $t\text{-C}_4\text{H}_9\text{O}^-$ in DMSO). The ease of this prototropy depends on the amine with phenothiazine > carbazole > diphenylamine > N-methylaniline. More recently Hubert and Viehe⁹ have reported the isomerization of N,N-dialkylpropargylamines with a catalyst made by dispersing potassium amide on alumina. It is possible to stop the isomerization at the allene



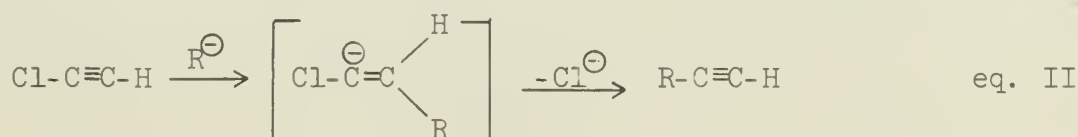
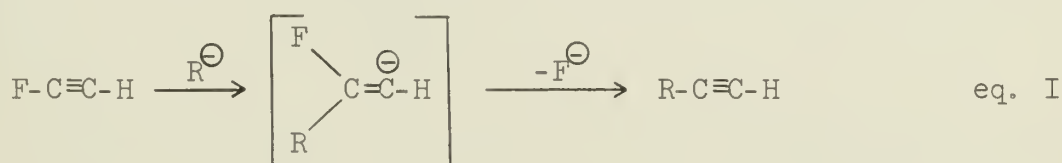
amine stage in most cases. However, the allene amine is unstable and tends to dimerize or polymerize easily under the conditions of the reaction. The fact that the ynamine is favored in the equilibrated mixture indicates that the disubstituted triple bond is more stable than the monosubstituted triple bond.^{10,11}

The second approach to ynamine synthesis, the joining of the acetylene group to the substituent, has been used successfully by several researchers. Wolf and Kowitz³ carried out the first planned synthesis of an ynamine in 1960. They allowed N-chlorodiethylamine to react in ether with phenylethynylmagnesium bromide and by water-free workup, obtained 1.7% yield of diethylaminophenylacetylene. They also postulated ynamine formation in the reaction of a lithium acetylide with N-chlorodiethylamine, but they were unable to isolate it in a pure form because of the water involved in the workup of the reaction. The reaction of acetylides with chloroamines is very limited in usefulness as seen by the low yields of product. The poor results are probably caused by the low reactivity of chloroamines in nucleophilic substitution of the chlorine.

Viehe had considerably more success in his preparation of ynamines by reacting haloalkynes with N,N-disubstituted alkali metal amides. For example the reaction of chlorophenylacetylene with lithium dimethylamide resulted in 87% yield of the ynamine.¹² Viehe found, however, that nucleophilic substitution of the halogen is



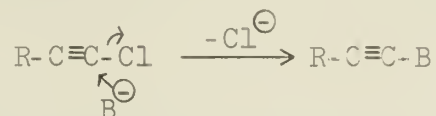
much easier in fluoroalkynes than in chloroalkynes. Diisopropylethynylamine can be prepared from lithium diisobutylamide only with fluoroacetylene and not with chloroacetylene.¹³ Viehe explained the variations in the reactivity of haloacetylenes in the following way. First, reactivity of an acetylene molecule increases with the increasing electronegativity¹⁴ of the halogen substituent attached at the electronegative sp carbon atom. Second, for chlorine or higher period elements stabilizing d-orbital resonance is possible so that a negative charge on the carbon atom α to the heteroatom may be delocalized. So while α -addition followed by facile β -elimination (eq. I) is likely for fluoroalkynes, with chloroalkynes the nucleophilic reagent may add to the β -carbon atom (eq. II) since the chlorine atom can stabilize the negative charge on the α -carbon atom. The chlorine atom must then be lost by α -elimination which is energetically less favorable. Chloroalkynes are only easily substituted then if the acetylene carries an electronegative substituent such as the phenyl group of the earlier example. Under the same conditions that chlorophenylacetylene reacts with lithium dimethylamide, t-butylchloroacetylene



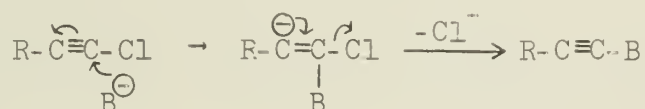
does not react. It reacts only in the strongly polarizing solvent hexamethyl phosphorus triamide (HMPT) giving the ynamine in about 70% yield.

As a result of his work with t-butylchloroacetylene, Viehe has proposed a new mechanism for nucleophilic substitution of halogen on triply bonded carbon atoms. The following three mechanisms had previously been proposed.

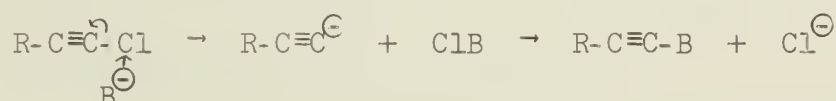
Direct substitution:



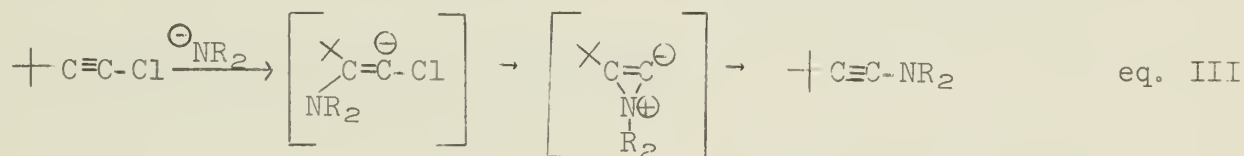
α -Addition and β -elimination:



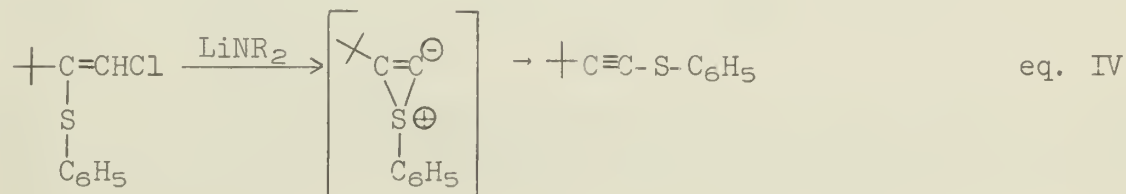
Attack on the heteroatom followed by direct substitution:



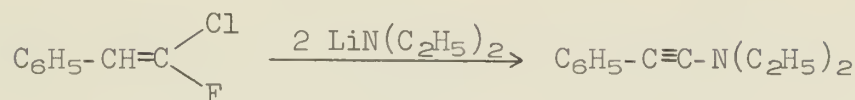
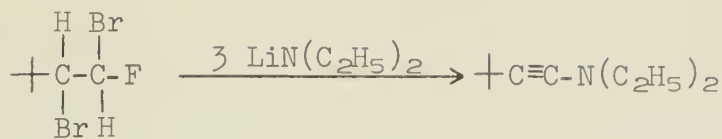
Direct substitution is unlikely because of the low reactivity of ethynyl halides. The C-Cl bond in chloroalkynes is much stronger than in chloroalkanes because of the increased electronegativity of the sp-hybridized carbon. The attack on the heteroatom proposed by J. F. Arens¹⁵ is possible only in a few special cases. For example, alkoxide as the base would lead to the little-reactive hypochlorites ROCl.¹³ α -Addition and β -elimination proposed by Ziegler and associates¹⁶ is therefore regarded as the most likely mechanism. Obviously, this mechanism cannot operate if a β -addition occurs instead of the α -addition. So when Viehe found that t-butylchloroacetylene does add phenoxide and thiophenolate at the β -position despite steric hindrance by the t-butyl group, he proposed that the nucleophilic substitution of haloalkynes occurs by β -addition, α -elimination, and what he called "onium rearrangement" (eq. III). Viehe cites a number of examples of "onium type rearrangements" to lend support to his mechanism.¹³ The thiophenolate adduct of t-butyl-



chloroacetylene may rearrange via "onium type intermediate" to give the acetylene derivative (eq. IV).

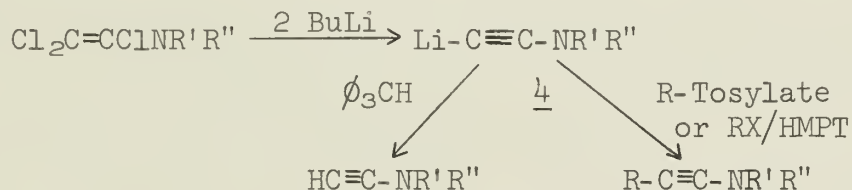


Although the fluoroalkynes were found to be best for the formation of ynamines by substitution they were not practical starting materials because of their limited availability. Viehe and associates reported, however, that dihalogenoalkenes and trihalogenoalkanes reacted with lithium amides to give ynamines.^{12,17} It is not known whether the haloalkyne is formed first and then the substitution occurs or whether the substitution occurs first followed by elimination to give the ynamine. Acetylene ethers may also be substituted with lithium amide to give ynamines in 60% yield.¹⁸



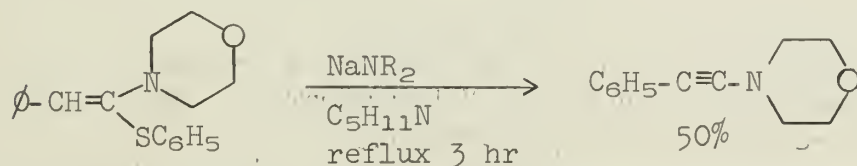
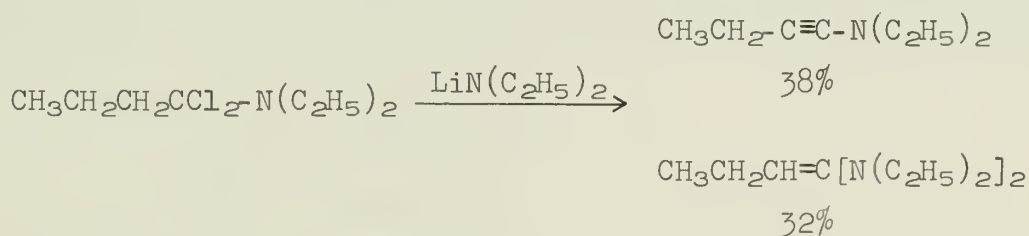
Viehe, Miller and Dickstein¹⁹ have also prepared ynamines by the reaction of halogenoalkynes and tertiary aliphatic amines. An initially formed ammonium salt eliminates halogenoalkane to give the ynamine.

Thirdly, several useful syntheses of ynamines involving elimination from suitably halogenated amines have been reported. J. Ficini and C. Barbara²⁰ have developed a general route to ynamine derivatives starting from trichloroenamines. The trichloroenamines can be prepared from trichloroacetic acid in 75% yield according to the method of Speziale.²¹ An initial attack of BuLi on a chlorine of the haloenamine is followed by elimination of a second atom of chlorine. The



intermediate chloroynamine immediately undergoes an acetylenic metal halogen exchange to give 4. The lithium acetylide has a low reactivity with respect to alkyl halogens so that it does not react under the conditions of the reaction with the BuCl present. It does react, however, with more reactive alkyl iodides, bromides, or tosylates in the solvent HMPT or mixtures of HMPT-ether. Average yields are 60-70% based on the enamine.

Ynamines have also been prepared from amide chlorides which are readily available from tertiary amides and phosgene.²² Often the yield of the reaction is poor because considerable alkenylidenediamines are formed along with the ynamine.¹³



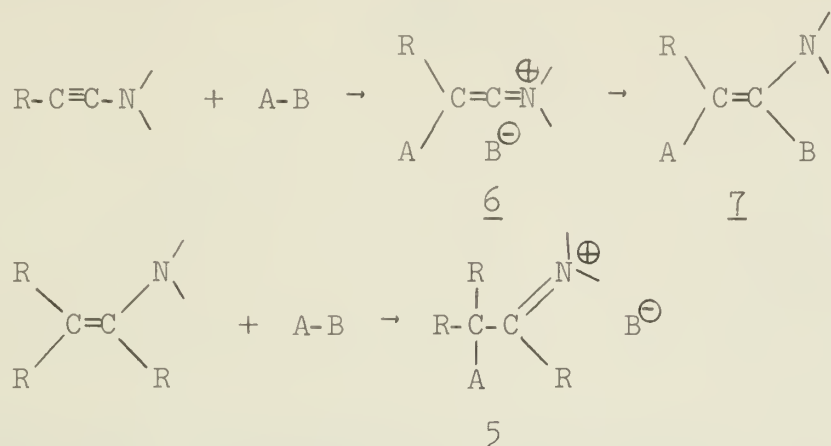
The elimination of thiolate from Ketene S,N-acetals has been used as a synthesis of ynamines.²² Yu. Yu. Tsmur and V. I. Ivanik²³ reported the synthesis of a bromoynamine by heating N,N-diethylbromoacetamide with PCl₅. So far this reaction has not been reproducible by other researchers.¹³

In conclusion, one must consider both the structure and the quantity desired of a given ynamine before choosing a synthetic method. The isomerization of a propargyl amine is probably the best for preparation of a fairly large quantity of a methyl ynamine. On the other hand, the synthetic route of Ficini and Barbara is the most useful in the preparation of a wide range of more complicated alkyl derivatives.

REACTIONS OF YNAMINES

Ynamines are good nucleophilic reagents; they are not however as reactive as

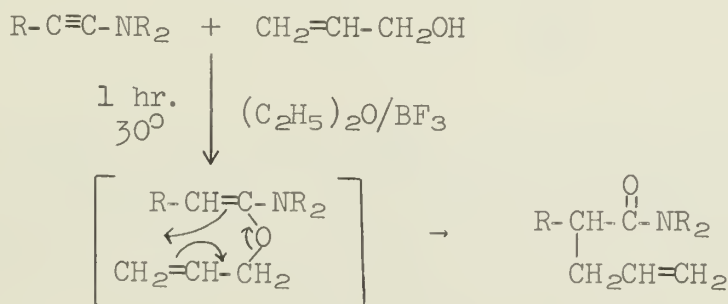
enamines in substitution reactions. While one obtains an aliphatic imonium salt 5 in nucleophilic reactions of enamines, ynamines give an energetically less favorable ketene-iminium function 6. Consequently, ynamines are more reactive with dipolar or electrically opposing bifunctional molecules where addition takes place at positions α and β to the nitrogen giving the more favored product 7.



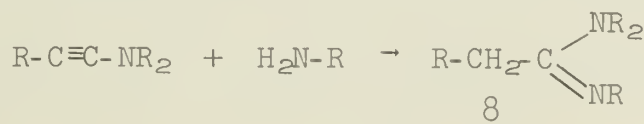
Ynamines also behave as electrophiles in many acid-catalyzed reactions. This is consistent with a ketene-iminium intermediate which reacts as an electrophile to form the more favored type product 7. The nucleophilicity of an ynamine is quite dependent upon the nitrogen substituents; as one would predict the N,N-dialkylynamines are stronger nucleophiles than the N,N-diaryl compounds.

Ynamines react with water to form amides.³ The reaction is exothermic when acid-catalyzed but many ynamines react in basic solution at room temperature. Ynamines are good dehydrating agents for the formation of acid anhydrides.²⁴ They were shown to be superior to such dehydrating agents as ethoxyacetylene and dicyclohexylcarbodiimide. Ynamines have also been used as dehydrating agents to form amides in peptide synthesis.²⁵ The yields are almost quantitative, but so far conditions have not been found to avoid at least partial racemization.²⁶

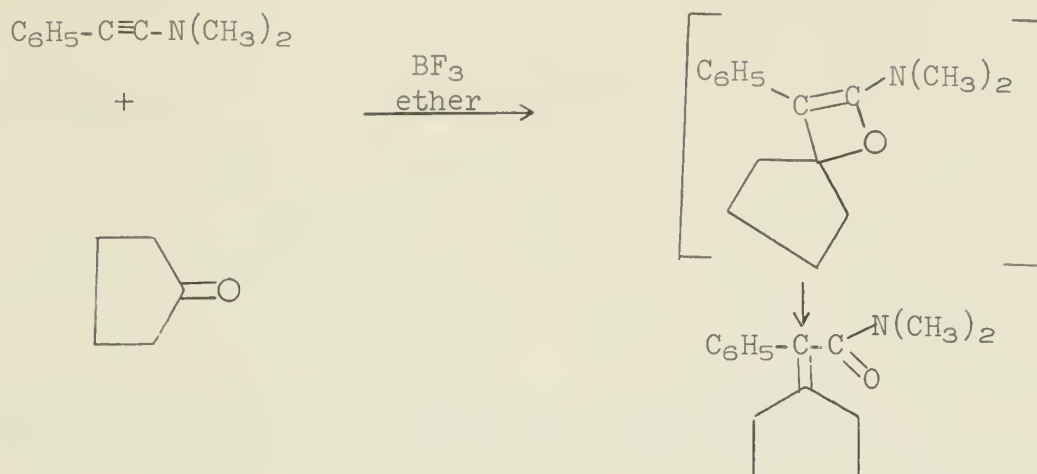
The addition of alcohols to ynamines occurs readily with acid or BF_3 catalysis.²⁴ An especially interesting example is the addition of allyl alcohols because of the Claisen rearrangement which follows the addition. J. Ficini and C. Barbara²⁷ reported yields of 50-85% of the γ -acrylamides in the reaction of ynamines with several primary allyl alcohols. This reaction is potentially useful for building complex carbon chains. However, with secondary or especially with tertiary alcohols, an elimination reaction predominates to give an amide and a conjugated olefin.



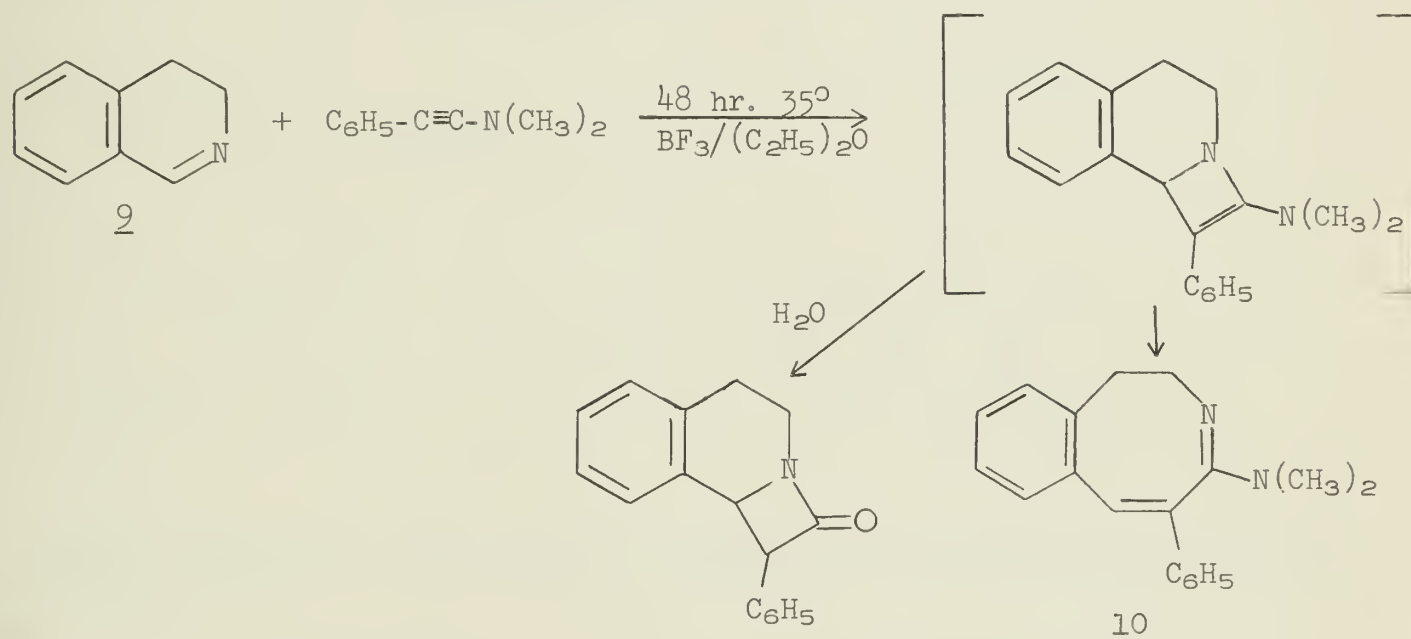
Primary or secondary amines also add to ynamines upon acidic catalysis similarly to alcohols.²⁴ Strongly acidic amines react more slowly probably because they hinder the formation of the ketene-iminium structure. A Claisen rearrangement is also possible for allyl amines, but it only occurs at higher temperatures (250°).¹³ The product of primary amine addition to an ynamine is an amidine 8.



Ketones,²⁸ quinones,²⁹ imines²⁸ and arylsulfonylimines³⁰ react with ynamines with BF_3 or acid catalysis to give α -acrylamides and amidines. The α -acrylamide



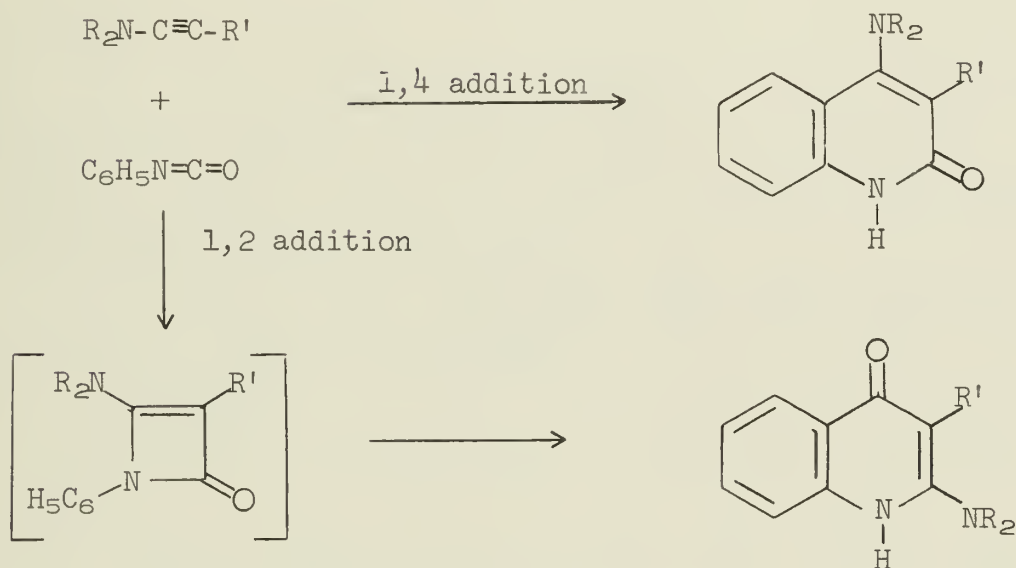
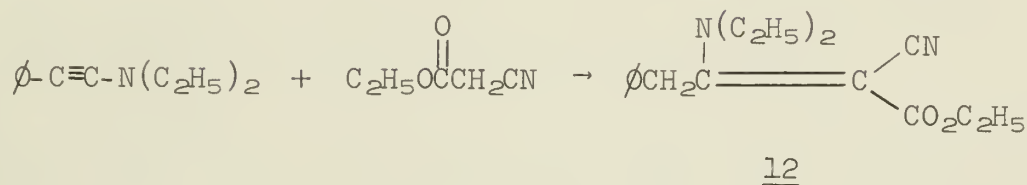
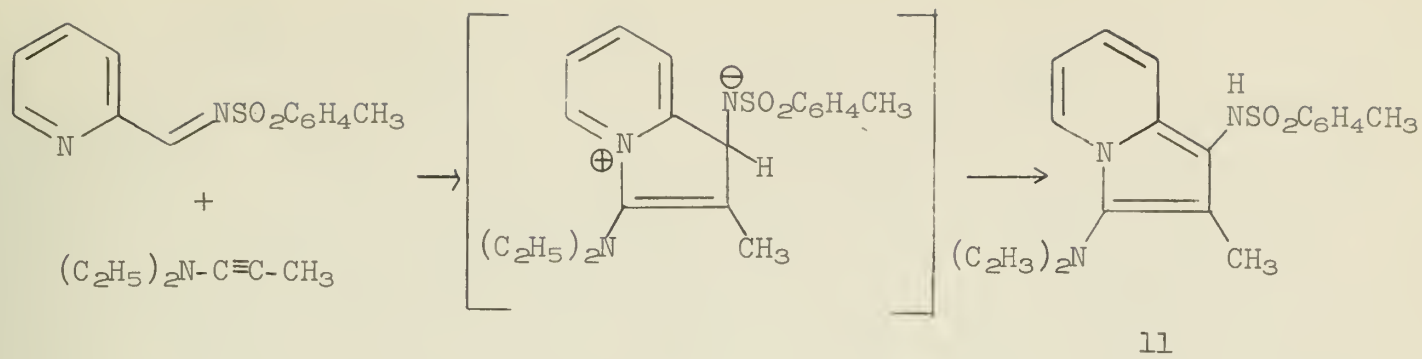
probably results from rearrangement of a four-membered-ring adduct formed by initial 1,2 addition. In the condensation of the cyclic imine dihydroisoquinoline 9 with an ynamine the intermediate four-membered-ring adduct can be detected by competitive hydrolysis.¹³ The reaction results in the expansion of the six-membered ring into the eight-membered ring of structure 10.



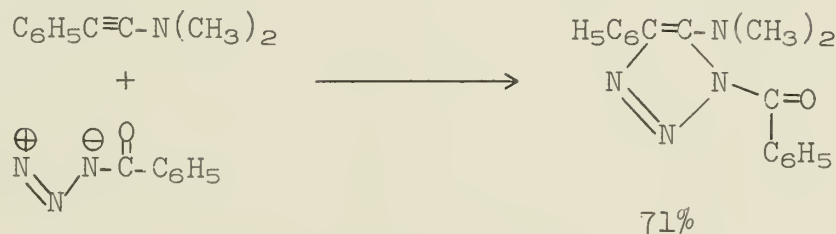
Kuehne and Sheeran³⁰ observed a rather remarkable deviation from the regular reaction path of ynamines and sulfonimides in the reaction of methylsubstituted ynamine with 2-pyridalsulfonimide. The formation of pyrrocoline 11 in this reaction seems to imply that the relative nucleophilicities of the nitrogens in the pyridal-sulfonimide, rather than in a zwitterionic cyclization precursor govern the course of the reaction. This reaction path therefore indicates a concerted addition mechanism for certain ynamine reactions.

Acidic carbon compounds add to ynamines as expected to give enamine derivatives.³⁰ Ethyl cyanoacetate spontaneously adds to N,N-diethylphenylethynylamine, for example, to give compound 12.

Ynamines react with phenylisocyanate by both 1,4 and 1,2 addition.³⁰ Although Ficini and Krief³¹ reported isolation of only 1,4 addition product, it now appears³⁰ that their structural assignments are incorrect and that they actually isolated products of 1,2 addition only. The product of 1,2 addition, 2-amino-4-quinolones, results from opening of the initially formed four-membered ring and subsequent cyclization. There is some evidence that the ratio of 1,4- to 1,2-addition product increases with increasing solvent polarity. This is consistent with the 1,2 addition occurring by a concerted mechanism and the 1,4 addition by a stepwise mechanism involving ionic intermediates.



Ynamines also react readily with 1,3 dipoles to give good yields of the expected product.^{28,30}



N,N-diethylphenylethynylamine undergoes a Diels-Alder addition to tetraphenylcyclopentadienone, yielding 7% of the decarbonylation product.³⁰

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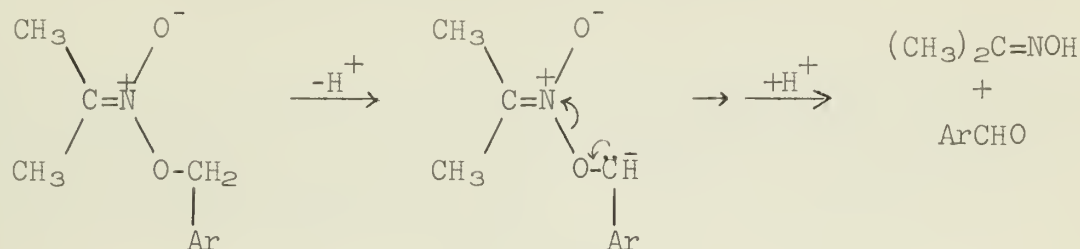
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ALKYLATION OF THE ANION OF 2-NITROPROPANE

Reported by Robert H. Williams

April 28, 1969

The treatment of an alkali-metal salt of 2-nitropropane with a para-substituted benzyl halide (other than p-nitrobenzyl chloride) results in the formation of the corresponding benzaldehyde.¹ The mechanism is believed^{2,3} to involve the base-catalyzed decomposition of the nitronic ester formed by S_N2 displacement of halide

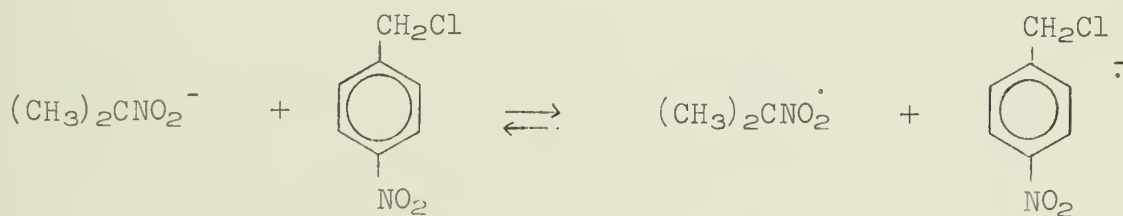


by one of the oxygen atoms of the anion.

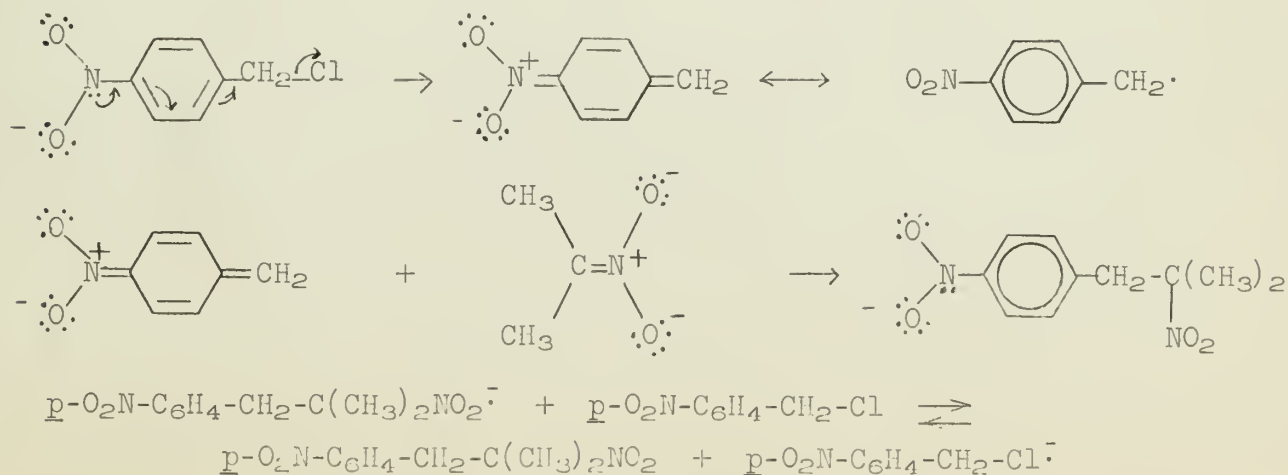
When a salt of 2-nitropropane is treated with o- or p-O₂N-C₆H₄CH₂X, the predominant product and rate of reaction are strongly influenced by the ease of displacement of the leaving group.^{4,5} When X is an easily displaced group^{6,7} (Br, I, OTs), the benzaldehyde is obtained in fair to good yield, and the rate of reaction is of the same order of magnitude as that of the unsubstituted compound. However, when the leaving group would be expected to be displaced with difficulty^{6,7} (Cl, N(CH₃)₃⁺, OCOC₆Cl₅), the product arising from alkylation at the carbon atom of the 2-nitro-2-propyl anion predominates, and the rate of reaction is greater than 100 times that for reaction of the unsubstituted compound.

The rate of carbon-alkylation is increased by illumination of the reaction mixture, and decreased by the presence of oxygen or aromatic nitro compounds. The extent of suppression of carbon-alkylation by an aromatic nitro compound increases with ease of polarographic reduction of the compound.^{5,8}

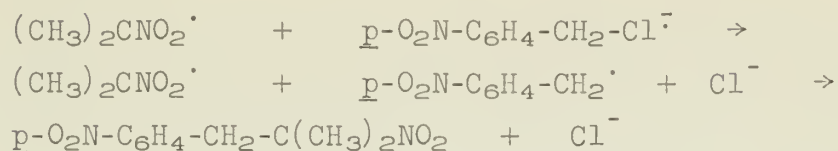
The first step in each of the recently proposed mechanisms for C-alkylation is an electron transfer from 2-nitro-2-propyl anion to p-nitrobenzyl chloride:



Russell and Danen⁸ postulate that the radical-anion is converted to products via a chain process:



Kornblum et al.^{5,9} have proposed a route which involves selective coupling (see footnote 21 in ref. 5) of the 2-nitro-2-propyl radical and the p-nitrobenzyl radical:



C-Alkylation of the 2-nitro-2-propyl anion by 2-halo-2-nitropropane and other halides has also been reported,^{10,11,12} as has C-alkylation of the anion of 2-carbethoxycoumaran-3-one by mononitrobenzyl halides.^{13,14} In each case, the proposed mechanism of reaction is the same as that proposed for C-alkylation of the 2-nitro-2-propyl anion by p-nitrobenzyl chloride.

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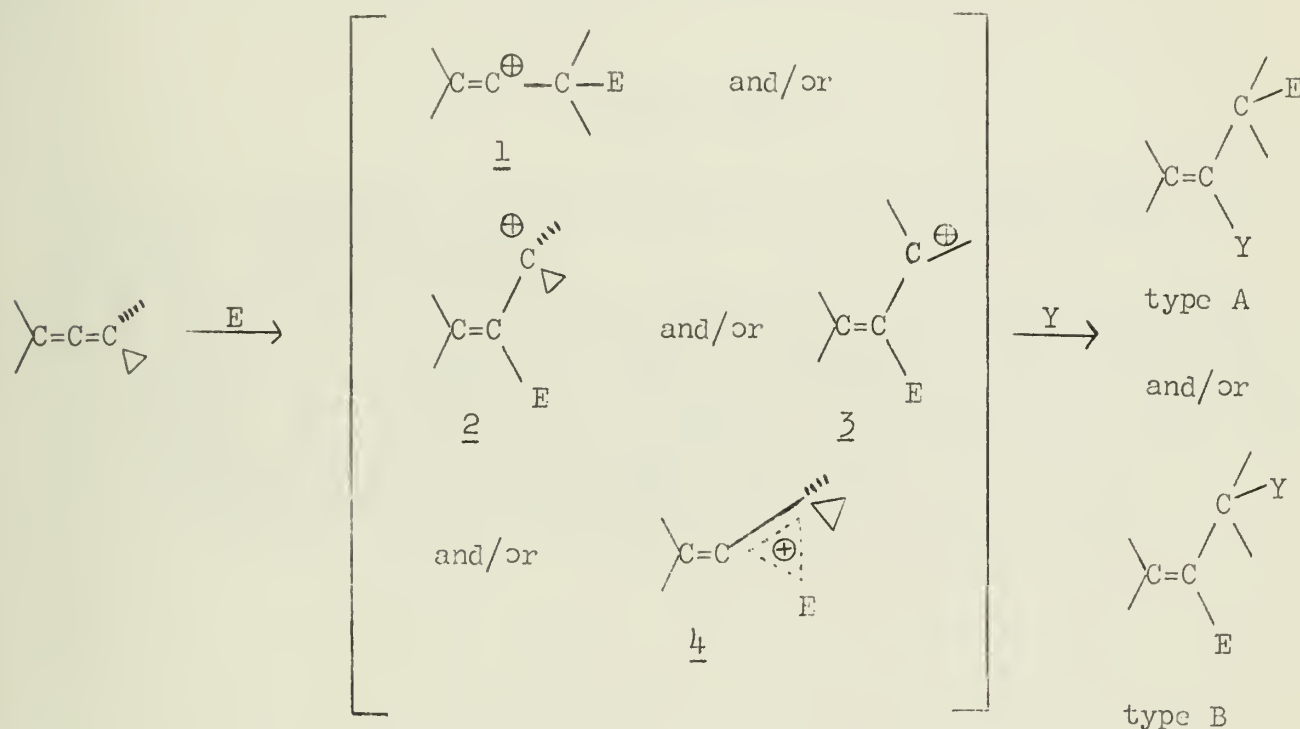
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SOME ASPECTS OF THE OXYMERCURATION OF METHYLATED ALLENES

Reported by Katie Thornburg

May 1, 1969

Electrophilic addition to allenes can lead to two basically different types of adducts. The electrophile E may become attached to either the terminal or the central carbon atom of the allenic system, affording a type A or a type B adduct, respectively. Suggested intermediates in an electrophilic addition reaction involving an allenic substrate include a vinyl carbonium ion, 1; a non-resonance stabilized allylic ion, 2; a planar conjugated ion, 3; and a bridged ion, 4.^{1,2,3} The situation is further complicated by the potential interconversion of these proposed intermediates.



The oxymercuration of allenes affords type A and type B adducts in nearly quantitative yield and is unaccompanied by the isomerization or dimerization occasionally found in other electrophilic additions to allenes.^{2,4} The methoxymercuration of di-, tri-, and tetramethylated allenes affords type B adducts.² Predominant addition occurs across the more highly substituted double bond, and, if geometrical isomerism is possible, the trans isomer is formed preferentially. These features of type B adduct formation are consistent with the intermediacy of a σ -bridged mercurinium ion which is nucleophilically opened in a trans stereospecific fashion. The results do not preclude the existence of other above-cited intermediates in this addition reaction.

Use of an optically active allene may allow dissymmetry in the reaction pathway to be detected.^{3,5,6,7} If no equilibration of the products occurs subsequent to their formation, the conversion of an allene of known configuration to a product of known configuration permits the stereochemistry of addition to be ascertained. Similarly, the conversion of an allene of known optical purity to a product of assessable optical purity can allow the extent to which dissymmetry is maintained during the course of addition to be determined. Observation of a degree of optical activity of the adduct comparable to that of the product essentially disallows the intermediacy of planar ions.

Levorotatory 1,3-dimethylallene has been assigned the R configuration on the basis of both experimental and theoretical lines of evidence.^{3,8} Treatment of this optically active allene with a methanolic solution of mercuric acetate results in an optically active mixture of cis and trans type B adducts.³ Configurational correlation of the asymmetric center in the predominant (trans) isomer with that in

(S)-(+)-trans-3-penten-2-ol has required conversion of both compounds to optically active 2-methoxypentane via transformations not affecting the asymmetric center in each case. The formation of the S saturated ether from the R allene is consistent with a trans nucleophilic opening of a dissymmetric bridged mercurinium ion. Although subject to experimental limitations primarily occasioned by the formation of 17% of cis product in the addition reaction, a comparison of the estimated optical purity of the starting material with the experimentally assessed optical purity of the transformed product indicates that the methoxymercuration of 1,3-dimethylallene is a highly stereospecific addition. By configurational and rotational correlation of the products of methoxybromination and methoxyiodination of (-)-1,3-dimethylallene with transformation products of the methoxymercuration mixture, it has been concluded that these additions exhibit similar stereospecificities.³

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